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HEMORRHAGIC DISEASE OF THE NEWBORN

A REPORT OF 358 CASES

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IN 1894 Townsend[43] first used the term "hemorrhagic disease of the newborn" to describe the spontaneous bleeding occasionally encountered in newborn infants, and he reported fifty cases from the Boston Lying-in Hospital. He was unable to determine the cause for the condition but recognized that he was dealing with a definite clinical syndrome. His observations have often been substantiated. Our concept of hemorrhagic disease has changed since his day. Originally the term implied any hemorrhage encountered during the neonatal period. Before the work of Grandidier[16] it was often confused with hemophilia. The ability of syphilis, infection, and primary blood disorders to mimic the condition was not well appreciated until the introduction of laboratory methods for diagnosis. It is still uncertain whether infants whose bleeding tendency has been revealed by trauma may properly be considered cases of hemorrhagic disease.[5, 6, 11, 17, 24, 28, 29, 39] Further diagnostic restrictions have been made by certain investigators. Time limits have been set for the occurrence of hemorrhage[6, 11, 17, 33] or pathologic changes in the bleeding, and clotting times have been required.[12, 13] Viewed in retrospect, these ideas seem somewhat artificial. The term is now usually reserved for cases in which hemorrhage is spontaneous and idiopathic.

The literature on hemorrhagic disease is voluminous and includes many short case reports. There are, however, a number of excellent reviews and general articles on the subject.[3, 7, 8, 9, 14, 26, 33, 34, 39, 44] It is not always easy to compare the data published by various investigators in view of their varying diagnostic criteria. However, they are in agreement regarding the basic facts. There are also a number of physiologic studies concerned with changes taking place in the neonatal period which might favor the occurrence of hemorrhage.

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In typical cases of hemorrhagic disease, bleeding begins on or about the third day of life and may occur from any part of the body, although the gastrointestinal tract is most often involved. A story of asphyxia at birth is strikingly frequent. The affected infant is normally large and robust, although a few authors have reported an increased incidence of prematurity. Hospital-born children are more often affected.[23, 43] The disease is most common in the winter and early spring months.[24, 29] Capon[5] is the only author to report the disease in both of twins. The mothers are more frequently primiparas of greater than the normal child-bearing age.[5, 9, 10, 22, 23] Without treatment the reported mortality varies between 27 and 80 per cent. In at least half the cases the disease is self-limited and recovery takes place spontaneously. The bleeding and clotting times may be prolonged. Transfusion with whole blood has come to be regarded as the most effective form of treatment.

There is adbundant evidence that newborn infants undergo changes in the early days of life which render them liable to hemorrhage. As many as 64 to 75 per cent may have occult blood in their stools.[2, 22, 32] There are concurrent changes in the bleeding and clotting times, which would appear to indicate a tendency to hemorrhage. Studies[1, 27, 34-36, 38] have also been made of blood calcium levels and such clotting factors as thrombin, thrombokinase, fibrin, and fibrinogen.

The etiology of hemorrhagic disease remains obscure, but the recent interest in vitamin K and prothrombin has led to the discovery of some highly suggestive facts. As early as 1912 occasional observations had suggested that bleeding in newborn infants might be associated with a lowered blood prothrombin.[15, 27, 37, 47] Using more reliable methods, Brinkhous, Smith, and Warner[4] confirmed this fact, as have Quick and Grossman.[31] The prothrombin level in the blood appears to drop below normal in the first twenty-four hours and does not rise again until the fifth day. These values are subject to considerable fluctuation, and no bleeding may take place even when the prothrombin is much reduced. Physiologic hypoprothrombinemia can be lessened or eliminated by feeding vitamin K to the mother or her child.[41, 45] This is true even for premature infants in whom prothrombin levels are apt to be unusually low.[21] Grossman[18] has reviewed this work recently. Cases of hemorrhagic disease have been reported with lowered blood prothrombin levels.[41] According to Waddell and Lawson,[46] less neonatal bleeding occurs in infants given prophylactic doses of vitamin K. A few cases of such bleeding appear to have been successfully treated with it.[30, 41, 46] Further work is needed before it can be stated categorically that hemorrhagic disease of the newborn infant is consistently caused by a lowered blood prothrombin. Until the normal prothrombin levels are better understood, it would seem unwise to use them as a measure of "potential hemorrhagic disease."

The therapeutic implications of vitamin K are obvious and intriguing and suggest that transfusion may eventually be discarded as the best method of treatment. Apparently transfusion does raise the prothrombin level in certain instances. If transfusion and vitamin therapy are to be evaluated fairly, it is necessary to have a reasonably clear idea of the results secured by each method of treatment. We therefore present data on a group of cases observed at the Boston Lying-in Hospital before and after the introduction of transfusion.

We have made an analysis of the cases of hemorrhagic disease occurring at the Boston Lying-in Hospital from 1874 to 1934 and at the Infants' Hospital in Boston from 1914 to 1937. The occurrence of unexplained spontaneous bleeding in the neonatal period was thought to warrant such a diagnosis. In instances where injury initiated bleeding we have taken only those cases in which the hemorrhage would ordinarily have been expected to cease promptly without any treatment. Infants with evidences of infection or blood dyscrasias were excluded. Children with intracranial hemorrhage were not included unless there was evidence of spontaneous hemorrhage elsewhere in the body. A detailed examination of individual hospital records was made, inasmuch as it was found that all cases in the hospital files did not conform to this classification. Only actual hospital admissions were considered, since the data on infants born in the Out-Patient Department were often not adequate. Data from the two institutions have been grouped when it seemed justified. The diagnostic attitudes, technique of study, and treatment used in the two hospitals were not strictly comparable until 1924, when there was included on the staff of the Boston Lying-in Hospital a pediatric house officer who was simultaneously on duty at the Infants' Hospital.

The validity of the diagnoses made on cases occurring before about 1915 may be questioned on the ground that laboratory data were lacking to exclude syphilis, sepsis, or erythroblastosis. However, a comparison of 133 cases observed in the pretransfusion era, 1874 to 1914, and 125 seen from 1915 to 1934 show no important statistical differences in the two groups. Whenever available, the autopsy records from both hospitals were consulted and cases found at necropsy not to be hemorrhagic disease were excluded.

INCIDENCE

Our series of 358 cases includes 258 infants from the Boston Lying-in Hospital. From 1874 to 1934 there were delivered in this institution (not including the Out-Patient Service) 48,691 live infants. This makes the incidence of the disease one in 188 deliveries or 0.53 per cent. There were 20,168 hospital admissions during the twenty-five years at the Infants' Hospital. The 100 cases which occurred during this time make an incidence of one in 202 or 0.5 per cent.

TABLE I

INCIDENCE BY FIVE-YEAR PERIODS IN BOSTON LYING-IN HOSPITAL

PERIOD	CASES	LIVE BIRTHS	RATE PER 1,000
1874-1879	4	958	4.17
1880-1884	3	1213	2.47
1885-1889	13	1757	7.40
1890-1894	19	2615	7.25
1895-1899	22	3117	7.06
1900-1904	13	3143	4.12
1905-1909	31	4014	7.73
1910-1914	28	4100	6.82
1915-1919	12	4296	2.79
1920-1924	19	4889	3.88
1925-1929	44	8633	5.10
1930-1934	50	9956	5.02
Total	258	48691	5.30

For the period 1935-39 the rate was 4.86 per thousand.

We have tabulated the cases from the Boston Lying-in Hospital by five-year periods in order to note any change in the incidence. The figures show considerable variation since 1874 with a lessened incidence in recent years.

In confirmation of previous observations we find some concentration of our cases during the winter months, although this is not sufficiently striking to be very significant. Thirty-two per cent occurred during the first three months of the year. Usually births at the Boston Lying-in Hospital reach a peak during the trimester from July to September. The fact that respiratory diseases are most frequent during the winter months may point to some relationship to infection. However, the hospital records do not reveal any relation between the occurrence of maternal sepsis and the incidence of hemorrhagic disease.

One pair of twins, both of whom had bleeding, was observed.

MATERNAL FACTORS

Previous authors have observed an apparent correlation between the occurrence of the hemorrhagic syndrome and those factors increasing maternal and fetal risk: increased age, primiparity, and operative delivery. The possible influence of maternal diet has also been suspected, and we now know that prothrombin levels in infants may be influenced by feeding vitamin K to their mothers. The mean age of our Boston Lying-in mothers was 27.5 years. Fifty-three per cent were primiparas as against 42 per cent for all hospital admissions to the same institution from 1931 to 1934. Nine per cent were negroes. Sixty-one and five tenths per cent had normal labors, and 27.8 per cent were delivered by forceps. The control figures at the Boston Lying-in Hospital for all deliveries from 1916 to 1933 are 61 per cent and 27.1 per cent, respectively.

Table II shows the frequency with which various types of delivery occurred in both institutions.

TABLE II

METHOD OF DELIVERY

DELIVERY	BOSTON LYING-IN		INFANTS' HOSPITAL		TOTAL	PER CENT	
Primiparous normal	74	61.5%	8	65%	82	22.9	62.7%
Multiparous normal	85		57		142	39.8	
Forceps	72		24		96	26.7	
Breech extraction	12		7		19	5.3	
Cesarean section	6		0		6	1.7	
Other	7		1		8	2.2	
Unknown	2		3		5	1.4	
Total	258		100		358	100.0	

The mothers of these children were not unusually subject to the complications of pregnancy or chronic disease. Two hundred and ten, or 81 per cent, of the Boston Lying-in mothers had normal pregnancies. Five and four-tenths per cent developed toxemia. There were three mothers with a past history of rheumatism or tuberculosis. Only one had had a previous child who developed hemorrhagic disease. No known cases of syphilis were included, but routine Wassermann tests were not done at the Boston Lying-in Hospital before 1920. No data bearing on maternal diet were available.

INCIDENCE OF ASPHYXIA

Since it has often been observed that asphyxia produces and predisposes to hemorrhage, we investigated its frequency. The criteria taken were cyanosis or pallor at birth, difficulty in resuscitation, or the passage of meconium in a vertex presentation.

TABLE III

INCIDENCE OF ASPHYXIA

HOSPITAL	ASPHYXIA	NO ASPHYXIA	UNKNOWN	TOTAL
Boston Lying-in	66	192	0	258
Infants' Hospital	11	57	32	100
Total	77	249	32	358

Of the Boston Lying-in series, sixty-six, or 25.5 per cent, showed gross signs of asphyxia. Normally, according to Clifford[11] and Javert,[23] one would expect to find an incidence of 3 per cent. The eightfold increase noted here would appear to be significant.

SEX DISTRIBUTION

One hundred and eighty-seven, or 52 per cent, of the children in the entire series were boys. For the Boston Lying-in series the figure was 53 per cent and for the Infants' Hospital, 49 per cent. This slight preponderance of males would be expected in any large series of births and supports the contention that sex is not an important factor.

SIZE OF INFANT

Some data were available concerning the physical maturity of these children. They were distributed by birth weight as shown in Table IV.

The mean birth weight for the Boston Lying-in children was 7 pounds 5 ounces and for the series as a whole, 7 pounds 6 ounces. This is slightly less than the mean birth weight of 7 pounds 8 ounces for infants at the Boston Lying-in Hospital. Similarly normal values were found for the circumference of the head and chest.

TABLE IV

BIRTH WEIGHT IN POUNDS

HOSPITAL	LESS THAN 5	5-6	6-7	7-8	8-9	9-10	10-11	11-12	12 OR MORE	UNKNOWN
Boston Lying-in Hospital	12	26	60	78	52	21	7	1	1	0
Infants' Hospital	6	8	18	31	18	6	5	1	1	6
Total	18	34	78	109	70	27	12	2	2	6

The incidence of prematurity, as measured by a birth weight of 5 pounds, was 5 per cent for the whole series. For the Boston Lying-in group it was 4.6 per cent or about 1.6 per cent more than the expected normal at that institution. It would not appear, however, that the incidence of prematurity was high enough in either group to account in any significant degree for the tendency to hemorrhage shown.

AGE AT ONSET

As has been noted by other observers, our patients showed a tendency to begin bleeding within the first three days of life.

TABLE V

AGE (DAYS) AT ONSET

HOSPITAL	LESS THAN 1	1	2	3	4	5	6	7	8 OR MORE	UNKNOWN	TOTAL
Boston Lying-in Hospital	22	28	50	69	36	17	13	4	11	8	258
Infants' Hospital	18	18	25	17	7	1	4	1	7	2	100
Total	40	46	75	86	43	18	17	5	18	10	358

About one-quarter of the patients began to bleed on the third day. Fifty-seven per cent of both series started on the second to fourth day, and eighteen, or 5 per cent, after the first week. The latest of these began on the fifteenth day.

It should be emphasized that cases of hemorrhagic disease may be seen as early as the first twenty-four hours of life. This was true in 11.2 per cent of our cases. These infants were characterized by an increased incidence of trauma or intracranial hemorrhage. Of twenty-three cases

beginning in the first twenty-four hours, thirteen gave external evidence of bleeding, usually from the gastrointestinal tract. There were seven cases of intracranial bleeding, of which two also had adrenal hemorrhage. The mortality was 66 per cent. Eleven patients received no specific treatment; ten of these died. The remaining twelve received rabbit serum (1) or transfusion (11), and, of these, five, or 41 per cent, died. These figures show increased mortality when the onset is early.

LOCATION OF BLEEDING

Hemorrhagic disease most often begins with gastrointestinal bleeding. One hundred and forty-six, or 40 per cent, of all our cases had hemorrhage from this location only. One hundred and fifty-seven, or 43 per cent, had bleeding from more than one site. Sixty-one, or 17 per cent, had intracranial hemorrhage in association with bleeding elsewhere in the body. Table VI gives some of the more unusual sources for hemorrhage and shows that almost any part of the body may be involved.

TABLE VI

UNUSUAL OR IMPORTANT SITES FOR BLEEDING

SITE	NO. OF CASES		
	INFANTS' HOSPITAL	BOSTON LYING-IN HOSPITAL	TOTAL
Purpura	9	0	9
Intracranial	18	43	61
Forceps marks	2	10	12
Tongue-tie cut	0	3	3—all fatal
Tongue	1	0	1
Circumcision wound	2	0	2
Retracted foreskin	2	0	2
Umbilicus	19	51	70
Adrenals	4	7	11
Vagina	5	2	7
Genitourinary tract (hematuria)	11	6	17
Renal	2	3	5
Intra-abdominal	1	0	1
Liver, subcapsular	0	1	1
Gums	1	0	1
Sclerae and conjunctivae	2	0	2
Hemothorax	1	0	1
Orbit	2	0	2
External auditory meatus	1	0	1

BLOOD FINDINGS

The laboratory data on our cases were usually limited to occasional blood counts and estimations of the bleeding and clotting times. The former showed nothing more than varying degrees of secondary anemia, and it was rare to find more than one count for a case. There were no demonstrable abnormalities in the white blood count or blood smears. The average bleeding and clotting times were increased, but an appreciable number of cases showed no variation from normal. In 107

cases in which the bleeding time was known it was normal in thirty-one, or about one-third. The average bleeding time was 10.5 minutes. The clotting time was known in 115 cases, and values of less than five minutes were seen in thirty cases. The average time was 10.6 minutes. The effect of asphyxia on the bleeding and clotting times was equivocal. Eighteen cases had an average bleeding time of 18.2 minutes (one case bled for 120 minutes) and an average clotting time of 10.2 minutes. Estimations of the bleeding and clotting times often did not indicate how severe bleeding would be.

TABLE VII

BLEEDING AND CLOTTING TIMES—BOTH SERIES

TIME (MIN.)	BLEEDING TIME CASES	CLOTTING TIME* CASES
0- 3	31	9
3- 5	20	21
5-10	28	40
10 or more	28	45
Total	107	115

*Capillary tube method used.

MORTALITY

Since 1874 the mortality from hemorrhagic disease at the Boston Lying-in Hospital has markedly decreased. One wonders what factors may have been responsible for the change. Beginning about 1925 there was a very sudden drop in the mortality, from figures as high as 78 per cent to less than 15 per cent.

It is difficult to explain this phenomenon satisfactorily, although the possible effect of certain factors should be mentioned. Diagnostic criteria became more clearly defined. It is probable that before 1920 infection was less often detected and its tendency to produce bleeding not well appreciated. The routine use of the Wassermann test began in this year and was probably instrumental in eliminating a few unsuspected cases of congenital syphilis. Second, improvements were made in the hospital. A new building was erected in 1923, and there was a sudden increase in the number of patients served. The appointment to the staff in 1924 of a pediatric house officer assured better care and facilitated treatment of infants. Third, transfusion for hemorrhagic disease came into general use. This method of treatment was first tried in 1909, but it was not employed with any continuity until 1916. Between 1915 and 1925, only eleven of thirty-one cases were transfused. Thereafter transfusion was given in nearly all instances.

Table VIII shows the trend in mortality since 1874.

The gross mortality for both series of cases was 34.8 per cent. For the Boston Lying-in Hospital it was 38.7 per cent and for the Infants' Hospital, 25 per cent. This difference in results may be due to the fact that almost all patients from the Infants' Hospital were treated with

TABLE VIII

MORTALITY BY FIVE-YEAR PERIODS, 1874-1934, BOSTON LYING-IN HOSPITAL

PERIOD	LIVE BIRTHS	DEATHS	CASES	MORTALITY (PER CENT)	RATE PER 1,000 BIRTHS	REMARKS
1874-1879	958	4	4	100.0	4.2	
1880-1884	1,213	3	3	100.0	2.5	
1885-1889	1,757	8	13	61.5	4.5	
1890-1894	2,615	7	19	36.8	2.6	
1895-1899	3,117	8	22	36.2	2.6	
1900-1904	3,143	6	13	46.2	1.9	
1905-1909	4,014	15	31	48.2	3.7	Transfusions begun in 1909, but not given routinely until 1916
1910-1914	4,100	14	28	50.0	3.4	
1915-1919	4,296	8	12	66.6	1.9	Routine Wassermann tests started in 1920
1920-1924	4,889	15	19	78.0	3.0	New hospital built in 1923
1925-1929	8,633	5	44	11.4	0.6	Pediatric house officer introduced in 1924
1930-1934	9,956	7	50	14.0	0.7	
Total	48,691	100	258	38.7	2.0	

For the period 1935-1939 the mortality was 14.7 per cent or 0.7 per thousand live births.

blood given parenterally. Ninety-nine of the Boston Lying-in patients failed to receive such treatment, whereas this was true of only six babies from the Infants' Hospital.

Without treatment the mortality for both series was 57 per cent. With blood given intramuscularly or subcutaneously it was 50 per cent, and with transfusion it was 17.7 per cent. For the Boston Lying-in series the mortality after transfusion was 14.9 per cent. Thirty-one patients were treated with rabbit or human serum with a mortality of 42 per cent. Results were somewhat better when transfusion was given after the intramuscular administration of blood. In thirty-two cases in which this was done the mortality was 31.2 per cent. We have no data as to the relation between mortality and the time when treatment was given. Table IX shows the mortality by form of treatment for both the Boston Lying-in and Infants' Hospital series.

TABLE IX

MORTALITY ACCORDING TO TREATMENT—BOTH SERIES

TREATMENT	NO. OF CASES	RECOVERED	DIED	
			NO.	PER CENT
None	107	46	61	57.0
Gelatin	13	10	3	23.1
Rabbit or other serum	31	18	13	42.0
Blood administered intramuscularly or subcutaneously	22	11	11	50.0
Blood administered intramuscularly and transfusion	32	22	10	31.2
Transfusion only	153	126	27	17.7
Total	358	233	125	34.8

These figures support the contention that transfusion is an effective form of treatment for hemorrhagic disease. However, their validity may be questioned on the ground that mortality is not dependent on the form of treatment alone, but on the source of the hemorrhage. Cases with intracranial or internal hemorrhage are more apt to have a poor prognosis. By "internal" hemorrhage is meant bleeding into viscera other than the gastrointestinal tract. Taking the Boston Lying-in cases and excluding those in which trauma was clearly an initiating factor, we found the mortality with intracranial hemorrhage was 58 per cent, with "internal" hemorrhage 82 per cent, with external hemorrhage (including the gastrointestinal tract) 35 per cent, and with hemorrhage from the gastrointestinal tract alone 29.5 per cent. This variation in mortality was found in both untreated and transfused patients, and the results were consistently much better following transfusion.

TABLE X

MORTALITY ACCORDING TO TREATMENT AND LOCATION OF HEMORRHAGE IN BOSTON LYING-IN SERIES (TRAUMA EXCLUDED)

LOCATION OF HEMORRHAGE	NO. OF PATIENTS	DEATHS		PATIENTS NOT TRANSFUSED	DIED (PER CENT)	PATIENTS TRANSFUSED	DIED (PER CENT)
		NO.	PER CENT				
Gastrointestinal	98	29	29.5	46	50.0	52	11.5
Intracranial	43	25	58.0	18	77.0	25	44.0
"Internal"	23	19	82.0				
External	191	67	35.0	94	49.0	63*	12.7

*Does not include thirty-four patients treated with rabbit serum or with blood given intramuscularly with a mortality of 41 per cent.

It has not been possible to find a sizeable group of patients treated without transfusion and occurring after 1915, when bacteriologic methods were adequate for the exclusion of infection. We have a small series of fourteen patients, ten of whom died from intracranial or internal hemorrhage, a mortality of 71 per cent.

Transfusion is not always immediately specific in these patients. An appreciable number require more than one transfusion. This was true in thirty-two cases in the total series. The mortality was 25 per cent. The 121 patients who were transfused only once had a mortality of 16.5 per cent. One child was given as many as four transfusions before recovery.

Although we have shown that severe bleeding may occur in the presence of normal bleeding and clotting times, their prolongation implies an increased risk to the child. Patients with a bleeding time of over two minutes had a mortality of 40 per cent (both series) and with a clotting time of over five minutes, a mortality of 23.6 per cent.

PATHOLOGY

Patients who die of hemorrhagic disease show no specific pathologic findings at autopsy. We have reviewed the protocols on thirty-one cases,

nineteen from the Boston Lying-in Hospital and twelve from the Infants' Hospital. The findings may be summarized as follows:

1. Eighteen patients showed evidence of gastrointestinal bleeding. In two instances no source for the hemorrhage could be found, and only once were actual ulcerations present. In the other cases the mucosa was injected in varying degrees. Bleeding was more frequent from the stomach and the upper intestinal tract. Five patients had hemorrhage from the nose and mouth; two, from the esophagus; six, from the stomach; seven, from the small intestine; and four, from the large intestine.

2. Sixteen patients showed hemorrhage into the lung parenchyma. One patient had hemorrhagic bronchopneumonia.

3. In fifteen cases there were intracranial hemorrhages. Four were subdural; one, extradural; six, subarachnoid; and five, in the brain substance.

4. There was occasional involvement of the serous surfaces and cavities. Five patients had hemorrhage into the pleura; six, into the peritoneum or peritoneal cavity; and two, into the pericardium.

5. The abdominal viscera were involved with the following frequency: adrenals seven, kidneys eight, liver five, spleen two, and bladder six times. Hemorrhages into the bladder were often petechial and most likely to be found in the region of the trigone.

6. There were five patients with hemorrhage into the skin or subcutaneous tissue; one of these had hematoma of the manubrium.

7. Two patients showed generalized petechial hemorrhages of the viscera.

8. Certain incidental findings should be noted. Six patients had a congenital anomaly of the heart. There were five instances of patent ductus arteriosus, two of patent foramen ovale, one of bicuspid aortic valve, and one of coarctation of the aorta. Other findings were miliary abscesses of the submucosa of the stomach in one case, one case each of fatty degeneration of the liver and kidneys, and one with early focal necrosis of the liver.

In view of the contention that intracranial hemorrhage predisposes to hemorrhage elsewhere in the body and especially in the gastrointestinal tract, it is interesting to note that, of the ten cases of intracranial hemorrhage, five were cases with gastrointestinal hemorrhage. In only one case were actual ulcerations found. There were no unusual findings in the umbilical vessels.

In the presence of such varied pathologic findings, it is impossible to say that hemorrhagic disease is an entity. There is no evidence that any one organ or organ system is consistently involved. In only one instance was there evidence of a deficiency syndrome such as scurvy, which might be expected to be accompanied by bleeding.

DISCUSSION

The data presented substantiate previous observations on hemorrhagic disease. However, we feel justified in discarding certain etiological theories. It is rare to find in the affected organ a definite bleeding point, ulceration, or other focal lesion accounting for the hemorrhage. Intracranial hemorrhage does not consistently accompany hemorrhage from the gastrointestinal tract. The low incidence of prematurity and the normal development shown by these children afford indirect evidence against the theory that their blood vessels are immature and therefore more subject to the effects of trauma and asphyxia. It still remains to be demonstrated that there is some specific structural defect in the blood vessels. The increased incidence of asphyxia may be of etiological importance. While it is not a consistent factor, one suspects that it frequently initiates hemorrhage, or in other cases brings out a latent hemorrhagic tendency. It is, however, only one of the possible factors responsible for the hemorrhagic syndrome. What is now called "hemorrhagic disease" is largely a matter of definition.

Transfusion appears to be of definite value in treatment. A fatal outcome is more likely in infants having asphyxia or intracranial or "internal" hemorrhage, and the results reported by any observer will depend on the frequency with which he observed these more serious forms of hemorrhagic disease. In this series the increased mortality encountered in untreated cases was apparently not due to such factors. There are, furthermore, a number of reports in the literature commenting on the remarkable rapidity with which hemorrhage has been seen to stop following transfusion. It may be that we are benefiting the child merely by replacing blood, but the amount given by vein is frequently quite small in proportion to the quantity of blood lost, and the results are dramatic none the less. Neither does it seem likely that the effects of asphyxia, trauma, or infection could be so quickly offset.

We have no data in any of these cases on the quantitative level of prothrombin. Present knowledge does not permit one to state categorically that these children regularly suffer from such a defect in the clotting mechanism. Evidence accumulating in the literature substantiates the hypothesis that there is very probably in some cases a prothrombin deficiency which can be relieved by the administration of vitamin K and that this drop in the prothrombin level occurs at least to a slight degree in most newborn infants. Normal prothrombin levels will bear further study. The evidence does not at the present time justify the conclusion that this prothrombin deficiency is a consistent finding or that cases of hemorrhagic disease can be treated satisfactorily by the administration of vitamin K. Until such proof is made available, transfusion should continue to be the treatment of choice in hemorrhagic disease.

A word should be said regarding the technique of transfusion. Unless the infant shows evidence of marked blood loss, 50 c.c. is usually an adequate amount. About 7 per cent of the cases will require more than one transfusion. As regards a choice of donor, it is apparently immaterial whether the mother, the father, or some other person is used. Donors might be changed in the event that the first one or two transfusions did not benefit the child. From a practical standpoint it does not seem to matter during the first two weeks of life whether the donor and the recipient are compatible. There is no recorded instance of a transfusion reaction during this period of life among infants born at the Boston Lying-in Hospital even though compatability tests have been omitted. Cross matching and the use of compatible donors is probably preferable, and this procedure has been followed routinely at the Infants' Hospital. Transfusion into the longitudinal sinus is not only unnecessary but dangerous.

The question as to whether it is worthwhile as a prophylactic measure to give whole blood intramuscularly is of practical interest. Heffernan[20] has made the only published observations on this subject. The data presented show that the mortality of cases treated with blood given subcutaneously alone is neither so high as the untreated cases nor so low as those given transfusions. However, bleeding has been observed to occur after the giving of such blood prophylactically. From 1916 to 1934 at the Boston Lying-in Hospital, two infants were observed who had been given blood intramuscularly directly after delivery and yet proceeded to develop hemorrhagic disease. We, therefore, conclude tentatively that blood given subcutaneously does have a limited value in the prophylaxis and treatment of hemorrhagic disease, but it is not to be relied upon in all cases. Its use would seem to be limited to circumstances where no one is at hand possessing the necessary technical skill to transfuse the infant or where time is an important factor. Transfusion is preferable even under conditions where the child may be continuously and closely observed for signs of bleeding. Occult bleeding may occur in the interim.

It is probably wise during the first week of life to refrain from any manipulation or operation likely to cause bleeding. There are two cases from the literature[19, 47] and two in this series where bleeding developed after manual retraction of the foreskin. One of these patients died. Of six cases occurring after circumcision (two in our series), one was fatal.[25, 40, 42, 48] Clipping the frenum for tongue-tie is also a procedure to be viewed with respect, for among our Boston Lying-in cases there were three instances where fatal bleeding was started by this procedure.

CONCLUSIONS

1. Data are presented on 358 cases of hemorrhagic disease, 258 from the Boston Lying-in Hospital from 1874 to 1934 and 100 from the In-

fants' Hospital from 1914 to 1937. Experience with these cases seems to show that the mortality in hemorrhagic disease may be reduced from 57 per cent without treatment to less than 20 per cent if transfusion is used. Cases with asphyxia or intracranial hemorrhage have a poorer prognosis.

2. Hemorrhagic disease does not appear to be a specific disease, but rather a clinical syndrome, unrelated to congenital syphilis, infection, or such blood disorders as erythroblastosis fetalis. Trauma and asphyxia both seem to be etiological factors of importance.

3. There is increasing evidence that prothrombin deficiency may be the cause of at least one form of hemorrhagic disease. More data are needed on the prothrombin levels in normal and bleeding infants and on the effect of maternal diet, transfusion, and vitamin K on these levels.

4. The relation between asphyxia and hemorrhagic disease of the newborn infant warrants investigation.

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CLINICAL STUDIES ON THE HARMLESSNESS OF AND TUBERCULIN REACTIVITY FOLLOWING B C G VACCINATION BY THE MULTIPLE PUNCTURE METHOD

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IN ORDER to overcome draining cold abscesses and suppurating local lymph nodes, which at times complicate the subcutaneous or intradermal injection of B C G, a new method for vaccination (multiple puncture) was introduced experimentally in 1934[1] and clinically in 1937.[2] This study is concerned with the harmlessness and reactivity to tuberculin over a period of three to thirty-nine months following this form of vaccination.

PROCEDURE

The infants used in the study were all born at the Cook County Hospital of Chicago, which draws its patients from the poorer colored and white districts. They were all from a supposedly nontuberculous environment, as determined by x-ray examinations of all known contacts. Control and vaccinated patients were chosen impartially, unknown to the mother. The newborn infants were vaccinated on the third to the seventh day of life. A physician visited the homes of the vaccinated infants and the controls alike during the first month. Many of the tuberculin tests were performed there. The infants were brought back to the clinic when 3 months and 1 year of age, and every six months thereafter. Nurses' visits were alternated with clinic visits.

VACCINE

The actual preparation of the vaccine has been described.[1] Differing from heretofore, the vaccine was diluted in varying concentrations of glycerine and put in capillary tubes, much the same as is vaccinia virus. Scarifying needles were placed in similar tubes, thus dispensing with syringes and injecting needles. The diluent used was Sauton* diluted to one-fourth strength, containing 1.5, 30, or 50 per cent glycerine. Cultural and animal studies made by Rosenthal and Brown[3] revealed that 30 to 50 per cent glycerine was bacteriostatic, but only slightly bactericidal for B C G. Increasing the concentration of B C G by one-half compensated for the bactericidal effect of the glycerine. The age of the Sauton culture varied from 17 to 21 days; the concentration of B C G varied from 3.5 mg. per 1 c.c. to 9.0 mg. per 1 c.c.

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*Sauton is a synthetic medium used to grow B C G; it contains aspergin, salts, and glycerine.

METHOD OF VACCINATION

As originally described,[2] a drop of vaccine was placed on the outer aspect of the alcohol cleansed arm, and thirty-five to forty-five punctures were made over an area 2 by 1.5 cm. The needle (similar to a sturdy sewing needle) was held between the thumb and index finger about 1.5 cm. from the point, the shaft being tangential to the skin. Pressure was exerted mainly by a downstroke of the thumb and was firm enough so that the needle point more than just pierced the skin, yet stayed in the superficial layers to avoid too much bleeding (single stroke method). A modification of the above (better applicable to children and adults) was as follows: Following the downstroke, the point of the needle engaged the skin in an upward movement (double stroke method). The use of two sites of thirty punctures each on the same arm was also tried.

TUBERCULIN TESTING

Reactions were considered positive only if induration was 10 mm. in diameter or over (in children under 4 weeks 8 mm.). All readings were made after forty-eight hours. Table I gives the amounts of tuberculin used for various age groups. If the reaction was negative to one dilution of tuberculin, the test was repeated with a more concentrated solution.

TABLE I

AGE	DOSE (MG.)
7 days to 22 days	0.1 to 1 O.T.
23 days to 3 months	0.1 to 0.2
3 months to 7 months	0.1
7 months to 14 months	0.2
14 months and over	0.5

TABLE II

RAPIDITY OF APPEARANCE OF A TUBERCULIN REACTION FOLLOWING A SINGLE VACCINATION BY THE MULTIPLE PUNCTURE METHOD

DAYS AFTER VACCINATION (INCL.)	NO. TESTED	NO. POSITIVE	PER CENT POSITIVE
7-10	37	0	0
11-13	57	8	14.0
14-16	44	21	47.7
17-19	34	15	44.1
20-22	11	8	72.7
23-31	30	29	96.6
32-54	53	51	98.1

Rapidity of Appearance of a Positive Tuberculin Reaction (Table II).—Varying the concentration of vaccine from 3.5 to 9.0 mg. per 1 c.c. in 1.5 to 50 per cent glycerine, using thirty-five, forty-five, or sixty punctures (in two sites) by the single or double stroke method, did not appreciably influence the precocity of the development of a positive tuberculin reaction. Males seemed to react earlier than females, and color played no role under the conditions of the experiment.

Table II is a compilation of the results in 258 infants, tuberculin tested within fifty-four days after vaccination, using all methods. The usual dose of tuberculin was 0.2 mg. O.T. Regardless of method, no patients reacted positively before ten days; about half reacted at fourteen to sixteen days; and practically all reacted after twenty-three days. The uniformity of results, irrespective of the wide variability of dose and technique, suggests either that only a few living organisms are required to produce the desired effects or that there is a relative insensitivity to tuberculin in the newborn infant.

Duration of Reactivity to Tuberculin.—The great majority of the children here reported have been tuberculin tested at 6 months, 1 year, and every six months thereafter. Thus, the duration of tuberculin reactivity cited actually signifies a continuous interval in the same children. The control group, followed from birth and drawn from a similar social order and living in the same districts of Chicago, serves as an indicator for the incidence of natural tuberculous infection.

TABLE III

RESULTS OF A SINGLE VACCINATION BY THE MULTIPLE PUNCTURE METHOD

GROUPS (MO.)	TOTAL NO. OF BABIES	TOTAL NO. REQUIRING REVACCINATION	TOTAL DEATHS	AUTOPSIES OBTAINED	EVIDENCE OF TUBERCULOSIS	TOTAL NO. TESTED WITH O.T. UP TO 1-200	NO. POSITIVE	PER CENT POSITIVE TO A SINGLE VACCINATION AT BIRTH
3- 7	484	1	2	2	0	413	412	99.7
8-13	313	0	2	1	0	246 (1)*	245	99.6
14-21	215	3	1	1	0	158 (1)	154	97.5
22-27	154	4	0			106 (3)	99	93.4
28-33	93	2	0			59 (7)	50	84.8
34-39	53	5	0			33 (2)	26	78.8

*Number in the parentheses refers to children who have reached this age group but were revaccinated previously.

In Table III the number and percentage of positive reactors to tuberculin following the multiple puncture method at varying time intervals are given. Practically all the vaccinated patients reacted to tuberculin within three weeks to twenty-seven months. Almost 80 per cent were still positive at 3.25 years. Of the 484 infants vaccinated, 413 were tested with tuberculin up to concentrations of 0.5 mg. Only those not reacting to this dose were considered negative and were revaccinated.

The incidence of natural tuberculous infection (Table IV) in the first two years is low (0 to 5.8 per cent), but after that time it rises rapidly (8.5 to 19.2 per cent). Because of this fact, reductions in the percentage of positive reactors must be made. It is notable that, although all of these children were supposedly from a tuberculous free environment, some did become infected. This can be readily explained by the results of a recent survey made by the Chicago Municipal Tuber-

TABLE IV

RESULTS OF TUBERCULIN REACTIVITY IN CONTROL INFANTS

GROUPS (MONTHS)	TOTAL NO. OF BABIES	TOTAL DEATHS	AUTOPSIES OBTAINED	EVIDENCE OF TUBERCULOSIS	TOTAL MANTOUX TESTED	NO. POSITIVE	PER CENT POSITIVE
3- 7	698	2	2	0	613	0	0
8-13	515	8	5	1	416	8	1.9
14-21	394	1	1	0	294	9 (8)*	5.8
22-27	271	0			199	8 (9)	8.5
28-33	182	0			120	4 (10)	11.6
34-39	80	0			52	3 (7)	19.2

*Number in parentheses refers to children who have reached this age group but were positive previously.

culosis Sanitarium, which disclosed that the morbidity and mortality in the districts from which these children come are exceedingly high.

A Comparison of the Results of the Tuberculin Reaction Following the Multiple Puncture and Intradermal Methods.—A comparison of the intradermal and multiple puncture methods was undertaken at the onset of this study. Newborn infants were alternated for vaccination by these two methods, including a similar number of controls. Later the intradermal route was discontinued. Thus, there were 191 infants vaccinated by the intradermal, 484 by the multiple puncture methods, and 698 controls.

For the intradermal injection, 0.012 to 0.02 mg. of the vaccine was injected by means of needle and syringe in the outer aspect of the left arm. The diluent was 0.1 c.c. in every case, and care was exercised to introduce the vaccine as superficially as was possible.

TABLE V

RESULTS OF A SINGLE VACCINATION BY THE INTRADERMAL METHOD

GROUPS (MO.)	TOTAL NO. OF BABIES	TOTAL NO. REQUIRING REVACCINATION	TOTAL DEATHS	AUTOPSIES OBTAINED	EVIDENCE OF TUBERCULOSIS	TOTAL NO. TESTED WITH O.T. UP TO 1-200	NO. POSITIVE	PER CENT POSITIVE TO A SINGLE VACCINATION AT BIRTH
3- 7	191	1	1	1	0	179	178	99.4
8-13	191	0	1	1	0	153(1)*	152	99.4
14-21	163	0	0			116(1)	115	99.0
22-27	108	4	0			79(1)	74	93.7
28-33	66	1	0			43(4)	38	88.4
34-39	43	1	0			25(4)	20	80.0

*Number in parentheses refers to children who have reached this age group but were revaccinated previously.

A. Reactivity to Tuberculin.—The number of cases under twenty days for comparison is small. Using 0.1 mg. O.T., four of five reacted positively following the multiple puncture method, and none of six cases in the intradermal group reacted. During the period of twenty-one to fifty-four days, all but one were positive in each group of twenty-

six and nineteen cases, respectively (0.1 mg. O.T.). Table V gives the results from three to thirty-nine months following vaccination. Compared to Table III (multiple puncture method) little differences are noted. With few exceptions, all reacted to tuberculin. Here, as with the group of Table III, 0.1 to 0.5 mg. O.T. was used; only a few were retested.

Compared to the reports of other investigators using other methods, the positive tuberculin reactions following the multiple puncture method appear sooner, last longer, and the percentage of reactions to tuberculin is higher.

A possible explanation for the precocity of the appearance of tuberculin reactivity following the multiple puncture method can be had from microscopic examination of the lesions in guinea pigs.[2] The organisms, by this method, can actually be introduced into the more cellular superficial layers of the skin, an impossibility by the syringe and needle method. Multiple, small, local lesions result; they are rapidly transformed into numerous tubercles, containing many giant cells. Necrosis, abscess formation, blocking of lymph nodes, and scarring are uniformly absent. On the other hand, because of the large number of organisms directed at one point with the intradermal method, an area of edema and necrosis surrounded by a dense wall of polymorphonuclear leucocytes develops at the site of inoculation. These cells are so numerous as to partially block the draining lymph channels, thus retarding drainage and promoting further necrosis. A local abscess develops, but usually drains to the outside. Tubercles form, but they are not numerous, and rarely are giant cells noted, indicating a decreased tissue response as compared to the above.

B. Complications.—Following a single intradermal injection of B C G, a nodule, 3 to 8 mm. in diameter, invariably developed after three to five weeks. Spontaneous evacuation or absorption followed, the process at times extending for one to three months or even more. The mothers were often apprehensive and complained. The draining axillary lymph nodes were occasionally palpable. Residual scars (3 to 8 mm. in diameter) were frequent up to three years, and occurred in 70 per cent of cases at six months, in 60 per cent at twelve months, and in 35 per cent at eighteen months to three years.

The lesions following the multiple puncture method never progressed to exceed pinhead-sized papules, resembling goose flesh. The site of inoculation was not easily discernible twenty-four hours to two weeks following the vaccination. At that time pinpoint to pinhead-sized macules appeared, which became papular by the fourth to the sixth week. These regressed rapidly without palpable scars or depressions, leaving smooth discolored areas in the skin. Such discolorations were noted in 47 per cent of cases at three months, in 39 per cent at six months,

in 14 per cent at one year, in 6 per cent at two years, and in 0 per cent at three years. Lymph nodes were palpable uniformly, two weeks after vaccination.

C. Revaccination.—In the multiple puncture group, seven (2.6 per cent) were revaccinated between fourteen and twenty-seven months, while four (2.0 per cent) of the 191 in the intradermal group were revaccinated (Tables III and V). Only those children not reacting to 0.5 mg. of O.T. were revaccinated. The number of children in the older age groups where the majority of the revaccinations were done is too small to draw definite conclusions as to the results of the two methods of administering the vaccine.

DISCUSSION

This work has been concerned mainly with the harmlessness of the vaccine and the reactivity to old tuberculin following vaccination. Regarding harmlessness, there have not been any complications or deaths from tuberculosis following vaccination. In the vaccinated group, numbering 675 between the ages of 3 and 39 months, seven died; six have been autopsied (Tables III and V). Of the 698 controls of similar age and environment as above, eleven died and eight were autopsied (Table IV). One control patient who died of tuberculous meningitis, diagnosed clinically, was not autopsied (spinal fluid clear, Pandy three-plus positive, cell count 60, dominantly lymphocytes*). A sibling of this child, aged 2 years and vaccinated, showed no evidence of tuberculosis by x-ray and physical examination. X-ray evidence of tuberculosis in the immediate family was not found. In the control group three additional children developed clinical and x-ray evidence of tuberculosis.

Reactivity to tuberculin is the only available method that is now at hand indicating immunity in tuberculosis. From an experimental and clinical standpoint it is generally agreed that a primary infection, if not in itself progressive, confers a certain immunity against a virulent reinfection. One of the manifestations of this immunity is an altered reaction of the host, so-called allergy. Negre and Bretey[4] of the Institut Pasteur injected guinea pigs with B C G by the multiple puncture method. They also modified this technique by making several 1 cm. long scratches through a drop of vaccine. After the tuberculin test became positive, these animals were injected with virulent human tubercle bacilli. They found that "guinea pigs thus vaccinated acquired a marked resistance to virulent tubercle bacilli" and that "the degree of immunity was at least equal to that conferred by the subcutaneous or intradermal injection of B C G." They noted a well-defined resistance nine days after vaccination and a well-established resistance at nineteen days. The immunity set in much sooner than by any other method and was directly associated with reactivity to tuberculin. Weill-Halle of France,[5] Birkhaug of Norway,[6] Sayé and Etcheverry of Uruguay,[7]

*Spinal fluid for culture misplaced.

Wallgren of Sweden,[8] and Sayago and Chattas of the Argentine[9] have recently begun to use this technique in infants. The first three named have verified the results here given as to the rapidity of development of a positive tuberculin reaction.

Clinically, a relationship of tuberculin reactivity and tuberculosis immunity is borne out by many workers. Kereszturi, Rosenberg, and Park,[10] found that in infants orally vaccinated with B C G, the mortality from tuberculosis was 1.1 per cent, as compared to 0.7 per cent in the parenterally vaccinated, and 2.6 per cent in the controls. The percentage of reactivity to tuberculin varied inversely as the mortality. In Wallgren's studies,[11] all infants vaccinated intradermally reacted to tuberculin before they were returned to their tuberculous environments. Not one developed tuberculosis, although 228 infants were exposed from seven to seventy-two months.

In adults it has been shown that nurses who have entered training with a healed primary complex, as discovered by x-ray examination and tuberculin testing, developed one-third to one-tenth as much tuberculosis as those who did not react to tuberculin on admission to training (Heimbeck,[12] Amberson and Riggins,[13] Badger and Spink,[14] Mariette,[15] Edwards[16]). Recently Brahdy[17] of New York reported that among colored student nurses of Harlem Hospital, who practically all had primary lesions, not one case of tuberculosis developed at 3.5 years, although they were exposed to open cases of tuberculosis constantly. In four other hospitals in New York City, employing white student nurses who frequently do not have primary lesions (30 to 66 per cent), 6.7 per thousand developed x-ray evidence of pulmonary tuberculosis.

The criticism of Myers',[18] Stewart's,[19] and Brailey's[20] interpretation of the high incidence of tuberculous deaths in children reacting to tuberculin is that these children most probably have come from a tuberculous environment and were repeatedly exposed, while the negative reactors most probably had had little or no exposure. A positive reaction in a child might also signify a progressive lesion not detected by the x-ray. It is well known from both experimental and clinical data that, whereas a single minimal infection which becomes quiescent produces a degree of immunity (Blacklock[21]), multiple minimal infections in quick succession may end fatally (Calmette and Guérin[22]).

B C G should not be expected to accomplish more than other forms of vaccination, where protection is afforded only against a casual contact with the respective disease and where isolation is strictly enforced. From statistics gathered by the Chicago Municipal Tuberculosis Sanitarium, 76 per cent of tuberculous children up to 16 years of age have no known history of contact with tuberculosis. Thus, the casual contact outside of the immediate family is responsible for three-quarters of tuberculosis infection in children. In the past year children from tuberculous homes have been vaccinated. In these cases isolation at

birth until the tuberculin test is positive is essential. Such children are returned to their homes only if the source case is considered closed as determined by several sputum examinations. Fortunately, a state law in Illinois requires that an open case of tuberculosis be separated from children under 16 years of age. In a recent report from New York City it was shown that tuberculin negative infants and children who had been exposed to open cases of tuberculosis and who were vaccinated and immediately returned to their environments gained little by this form of vaccination. This is not surprising, as no other form of vaccination would be effective under similar conditions. On the other hand, where isolation before and after vaccination was carried out, the mortality was three times as high in the nonvaccinated group.[23]

SUMMARY

In 675 newborn infants vaccinated with B C G by the multiple puncture or intradermal methods and followed for three to thirty-nine months, there have been no ill effects that could be ascribed to the vaccine.

In 258 newborn infants vaccinated on the third to tenth day of life with B C G by the multiple puncture method and tuberculin tested within the first fifty-four days following vaccination, it was found that 14 per cent reacted to old tuberculin at eleven to thirteen days, 47.7 per cent at fourteen to sixteen days, 96.6 per cent at twenty-three to thirty-one days, and 98 per cent at thirty-two to fifty-four days.

The duration of the reactivity to one vaccination by the multiple puncture method was 99.7 per cent at three to seven months, 99.6 per cent at eight to thirteen months, 97.5 per cent at fourteen to twenty-one months, 93.4 per cent at twenty to twenty-seven months, 84.8 per cent at eight to thirty-three months, and 78.8 per cent at thirty-four to thirty-nine months.

In the nonvaccinated infants living under similar conditions and followed exactly as above, the reaction to tuberculin was 0 per cent at three to seven months, 1.9 per cent at eight to thirteen months, 5.8 per cent at fourteen to twenty-one months, 8.5 per cent at twenty-two to twenty-seven months, 11.6 per cent at twenty-eight to thirty-three months, 19.2 per cent at thirty-four to thirty-nine months.

The percentage of positive reactors in newborn infants was not appreciably altered if 3.5 to 9 mg. of vaccine diluted in one-fourth strength Sauton containing 1.5 to 50 per cent glycerine were used.

Colored and white newborn infants reacted alike to the vaccine and to tuberculin.

A comparison of the multiple puncture and intradermal methods of vaccination revealed that the former is simple in application (needle and vaccine are dispensed in capillary tubes; syringe and injecting needle are eliminated) and yields fewer complications. The reactivities to tuberculin following both methods of administration are comparable.

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DIABETIC CHILDREN IN NONDIABETIC CAMPS

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IT HAS been demonstrated that diabetic children who are receiving adequate medical treatment can be normally active and that physical activity within ordinary limits may actually be beneficial. For these reasons special camps for diabetic children have become increasingly popular in recent years and are making important contributions in providing the means for a vacation period as well as in demonstrating to a still somewhat doubtful public that diabetic children can lead essentially "normal" lives.

Except in the larger metropolitan areas, however, there is not a sufficient number of diabetic children to justify the maintenance of a special camp,[1] or, if a camp is conducted, the range in age is likely to be so great that there are difficulties in providing an adequate camp program. This has been our experience. In 1936 a special camp was conducted in Cincinnati for about thirty diabetic children. There was no particular difficulty in securing financial aid from a few philanthropic citizens, and an ideal site with adequate buildings, swimming pool, and playground was procured. While there was practically universal accord that the camp was a highly successful venture, it was obvious that a more satisfactory camp program could be provided by limiting children to a narrower age range than 7 to 18 years. Segregation by sex is not important for children from 6 to 8 years of age, and a group of ten to twelve children of this age range is adequate for a satisfactory camp program. In the case of older children, however, segregation of the sexes is desirable, and there should be a sufficient number of children to play competitive games as well as to conduct several different activities at one time.

Prior to 1936 we had attempted to persuade the executive officers of several general camps to include a few diabetic boys and girls in their quota. With the exception of one camp in which one boy was accepted, these efforts were unsuccessful. In 1939 the director of the Cincinnati Camp for Girl Scouts agreed to take eight diabetic girls. The trial was so satisfactory that it was repeated in 1940, when nine diabetic girls attended the camp. On the basis of this experience the camp personnel is completely convinced that diabetic children can be included in a camp which is designed primarily for "normal" children.

The camp should be well conducted and, in addition to a carefully balanced program, should have adequate health supervision. The latter should include medical examination immediately prior to admission to

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the camp, a capable graduate nurse in attendance, a physician either in residence or in close proximity, and a good dietary department. The camp which has been mentioned employed a graduate dietitian but felt that she should not assume the extra load of supervision of the diabetic diets, and so an additional dietitian was added to the personnel. The entire personnel was acquainted with the problems peculiar to diabetic children, and the counselors immediately in charge of them had special instruction, particularly in reference to the symptomatology and the treatment of insulin shock. As part of their camp duties the children assisted in the measuring of their food, the examination of urine, the administration of insulin, and the keeping of records. Urine specimens were collected before each of the three meals and examined at the time of the last collection.

The diets of the diabetic children were adapted from the regular camp diet and did not vary greatly from it. The comparative diets for a single day are shown in Table I. Only two quantitative diets were employed for the diabetic girls, one for the larger girls and another for the smaller ones. In order to lessen the likelihood of insulin shocks, fruit was provided at 7 A.M. and again at 10 A.M.

TABLE I

EXAMPLE OF DAILY MENU

DIET FOR REGULAR CAMPERS	DIET FOR DIABETIC GIRLS
Canteloupe	Canteloupe
Cream of Wheat	Cream of Wheat
Pancakes with syrup	Poached egg
Butter	Toast and butter
Milk	Milk
Hamburger on buttered bun	Hamburger on buttered bun
Spaghetti with tomatoes	Spaghetti with tomatoes
	Peas
Coleslaw	Coleslaw
Watermelon	Watermelon
Milk	Milk
Cottage cheese	Cottage cheese
Sliced tomatoes	Sliced tomatoes
Bread and butter	Bread and butter
Boiled potatoes	Boiled potatoes
Fruit jello	Sliced oranges and fresh peaches
Milk	Milk

Seven of the nine girls received separate injections of protamine zinc insulin and regular insulin once daily before breakfast; one, protamine insulin only; and the other girl received two injections of regular insulin daily. Those who received protamine and regular insulin had their total dosage reduced on the first day of camp, and subsequent reductions were made in the total daily dosage of insulin for all of the girls during the two-week camp period. One girl who received 20 units of protamine zinc insulin daily prior to the camp period had her dosage gradually reduced until injections were eliminated entirely for the last two days

in camp. At no time did she have more than a trace of sugar in the urine. Six of the girls had a total of fifteen shocks, most of which were very slight and practically all of which occurred in the first week of camp life.

The attitude of the camp personnel was entirely favorable to the inclusion of the diabetic children and is expressed by the camp director[2] as follows: "After a two year trial of providing camping experience for the children with diabetes . . . I am convinced that many camps could offer a similar experience to children with this disease. . . . In our camp the difficulty with adjustment did not arise so much from the physical handicaps as from the needs for social adjustment. In other words, any child from similar family backgrounds could have presented the same problem in adjustment. . . . Selection of counselors capable of giving careful, constant supervision is of paramount importance. . . . Many counselors on our staff asked for the privilege of working with these girls since they regarded it as an especially interesting opportunity. . . . The diabetic girls were included in every type of camp activity including over night hikes and cookouts. . . . The second year, when the staff had more confidence . . . and when the children had made the important initial adjustments . . . we found much less difficulty in the integration of the groups in which they camped."

SUMMARY

A small group of diabetic girls was included as regular campers in a Girl Scout camp for two-week periods in two successive summers. In localities where special camps for diabetic children are not available, it is recommended that diabetic children be admitted to established camps which have adequate health supervision. While it is not assumed that regular camps are superior in all respects to special camps for diabetic children, they do have one advantage which is worthy of consideration; namely, the opportunity for diabetic children to live and to compete on an equal basis with nondiabetic children.

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SICKLE-CELL ANEMIA COMPLICATED BY ACUTE RHEUMATIC HEART DISEASE AND MASSIVE CEREBRAL HEMORRHAGE

Report of a Case

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THE case to be presented is one of sickle-cell anemia in which each of two complicating factors is, in our opinion, of sufficient interest to warrant discussion. First, in addition to the sickle-cell anemia there was a coexisting acute rheumatic heart disease, the presence of which was diagnosed clinically and proved at autopsy. Second, an unusual cerebral complication, massive hemorrhage, resulted in the sudden death of the patient.

The confusing resemblance of the symptoms of sickle-cell anemia and acute rheumatic fever is well known. Josephs[1] emphasized the incidence of joint symptoms similar to those of rheumatic fever. Yater and Hansmann[2] pointed out that a history of joint pains, with or without fever, the presence of an enlarged heart, the finding of a systolic precordial or mitral murmur, and the discovery of an enlarged liver frequently lead to the diagnosis of rheumatic heart disease in cases of sickle-cell anemia. Anderson and Ware[3] reported that all of the above listed symptoms occur in a large percentage of cases of sickle-cell anemia. Diggs and Ching[4] said that clinically organic heart disease is often suspected, but at autopsy there are no constant changes except those explicable upon the basis of anemia. Hamman[5] reported a case of sickle-cell anemia in a 5-year-old negro girl who was thought by several excellent clinicians to have, in addition, organic heart disease. At autopsy the heart was found to be perfectly normal. The clinical decision as to whether sickle-cell anemia alone is present, or whether there is accompanying rheumatic heart disease is made even more difficult by Cooley's statement, "Organic heart disease is about as common here [in sicklemia] as in any group of children subject to tonsillitis as these children often are."[6]

In our case, the clinicians who saw the patient held different opinions, although the majority felt that the child had organic heart disease. At autopsy there was unquestionable evidence that the patient had an acute rheumatic myocarditis with a chronic and acute mitral and tricuspid valvulitis.

Disorders of the central nervous system complicating sickle-cell anemia have been noted with increasing frequency of recent years. Syden-

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stricker, Mulherin, and Houseal[7] reported the occurrence of hemiplegia and convulsions in a 5-year-old negro boy, and since that time (1923) accounts of similar cases with neurological symptomatology have been numerous.[2, 8-19]

However, pathologic data are relatively meager. Graham,[8] in the course of post-mortem examination of a 30-year-old negro male, noted only a yellow tinge to the cerebrospinal fluid. Marked gyral flattening and an excess of subarachnoid transudate were found in a case reported by Hargrove and Mathews.[12] Penna de Szevedo[16] and Ford[17] have presented examples of thrombosis of the dural venous sinuses and pial veins. Hemorrhagic infarction of the cerebral parenchyma complicated the case of the latter author. A large subarachnoid hemorrhage and old fibrotic occlusion of the surface arteries of the brain were found by Arena[19] in a male negro of 4 years. Post-mortem examination of the brain of a 38-year-old negress with sicklemia by Yater and Hansmann[2] disclosed the presence of phagocytes filled with blood pigment around the pial vessels and the marginal zone of the cortex, as well as sclerosis and calcification of the choroid plexuses. The clinical course of Cook's case,[10] that of a negro male of 7 years, was featured by sudden unconsciousness, coma, and flaccid paralysis of the left side. Encephalomalacia in the right frontal lobe was the principal pathologic finding.

A detailed and comprehensive presentation of cerebral lesions in sickle-cell anemia was published recently by Hughes, Diggs and Gillespie.[20] These authors have documented six cases, in two of which post-mortem examination was permitted. In the first of these latter, that of a negro boy 6 years of age, gross and microscopic inspection of the brain revealed multiple thrombi in large and small blood vessels, with occasional proliferation of the endothelial lining of the arterioles. The left middle cerebral artery was completely occluded by an organizing red cell clot. The surface of most of the right hemisphere was atrophic and covered by a fibrosed arachnoid which contained hemosiderin. In histologic preparations of the cortex there was evident both diffuse and localized necrosis of ganglion cells, with glial repair. The patient had had epileptiform seizures and a left hemiparesis during life. In the second case, that of a 26-year-old negro who died in "uremia" and had experienced a "stroke" with residual paralysis of the right arm and leg twenty years before death, the left cerebral cortex exhibited an old infarct which mapped out the distribution of the superficial branches of the middle cerebral artery. The capillaries of the region were distended with sickled erythrocytes; there were hyperplasia of arteriolar lining cells and hyalinization of the walls of these vessels. Free and phagocytosed iron pigment lay in the meshes of the scarred leptomeninges.

From consideration of the above described changes the opinion was expressed that a combination of stasis and anoxemia had led to intimal

damage and thrombosis of cerebral vessels, resulting in rupture or fibrosis and ensuing parenchymal injury.

In the case to be reported by us the neuropathologic findings are at variance with those just described in that focal ganglion cell loss in the cerebral grey matter was not accompanied by occlusion of the vessels nourishing the regions involved. Moreover, mural vascular changes were minimal. Most striking was the discovery of a huge intracerebral hemorrhage, exactly similar in appearance to those seen in the brains of adults with hypertensive cardiovascular disease. This hemorrhage originated in the right basal ganglia and had ruptured into the ventricular system.

CASE REPORT

T. S., a 12-year-old negro male, was admitted to the Children's Clinic of the New Haven Hospital on Feb. 19, 1940, because of pneumonia.

History.—The family history was noncontributory. The first admission to the New Haven Hospital was in January, 1931, at which time the boy had bronchopneumonia. The clinical impression was corroborated by the roentgenographic findings. The heart was found to be enlarged to the left, and there was a loud, blowing, precordial systolic murmur. The spleen was palpable two fingerbreadths below the costal margin. The blood Kahn and Wassermann reactions were negative. The erythrocyte count was 2,020,000 cells per cubic millimeter; and the hemoglobin, 5.2 Gm. per cent. There were 35,000 white blood cells per cubic millimeter, 85 per cent of which were polymorphonuclear leucocytes. A wet preparation of the blood revealed marked sickling of erythrocytes at the end of two hours. The fragility test showed hemolysis beginning at 0.44 and complete at 0.32; the icterus index was 5; and there were 14 per cent reticulocytes. It was felt that the child had sickle-cell anemia in addition to respiratory infection. He was treated symptomatically and was also given three transfusions. The temperature, which on admission was 40.2° C., ran a remitting course for four days and then dropped precipitously to normal. The child seemed much better, but the blood count remained the same. Convalescence was marred by an uncomplicated linear fracture of the skull which was sustained when the child fell out of bed.

The child was next seen in the Children's Clinic in November, 1933, because of frontal headaches of one year's duration. These headaches appeared every two or three weeks, had their onset in the evening, and were relieved by a short nap. Physical examination at this time showed a chronically ill negro boy of 6 years with a temperature of 38.4° C. The heart was enlarged, and there was a loud precordial systolic murmur transmitted well into the axilla and to the neck vessels. The mitral second sound was duplicated. The throat was normal in appearance; the lungs were clear to percussion and auscultation; and the spleen could not be felt. The red blood count was 1,640,000 cells per cubic millimeter; hemoglobin, 3.8 Gm. per cent. Sickling was visible in wet preparations. The white cell count was 28,000 cells per cubic millimeter, with 72 per cent polymorphonuclear leucocytes. Bed rest and the daily administration of liver and ferric ammonium citrate were prescribed.

The patient was not seen again on the Pediatric Service until he entered the hospital on Feb. 19, 1940, with the chief complaints of fever, nosebleeds and joint pains. An interval history showed that the boy had not been well. He went to school daily, but usually came home tired and went to bed. Two years previously he had what the mother described as a "shock," with a transient right-sided hemiplegia which entirely cleared within two weeks' time. Two weeks before hospitalization he became feverish and had a slight hacking cough. One week before admission his right knee became swollen and painful. This process did not remain localized, but

involved in succession the right hip, ankle, shoulder, and sternoclavicular joint. On the day before admission he became quite feverish and was seen by a doctor who found signs of pneumonia and advised hospitalization. The following day, after a severe nosebleed, the boy was admitted to the New Haven Hospital.

Examination.—The temperature was 38° C.; the pulse, 172 per minute; respiration, 54 per minute; the blood pressure, 90 systolic and 30 diastolic. The boy's appearance was that of an emaciated, acutely and severely ill negro of 12 years. He was strikingly pale. The respirations were rapid and grunting, and there was a frequent, tight cough. The veins of the neck were pulsating, and there was a heaving cardiac impulse. There were blood crusts around the nares and a clot in the right nostril. The tongue was slightly coated; the teeth were yellow and carious; the throat was innocuous; and a clot of blood was present on the posterior pharyngeal wall. Percussion of the thorax showed a slightly impaired note over the left base posteriorly; on auscultation a few moist râles were heard over both bases. The heart action was tumultuous, but there were no palpable thrills. The point of maximum impulse lay in the sixth interspace in the midaxillary line, 11.5 cm. from the midsternal line. The right border of cardiac dullness was 3.5 cm. from the midsternal line. Both heart sounds were heard over all valvular areas. There was a loud, blowing systolic murmur heard all over the precordium and at the base where the murmur ended in a clapping second sound. From apex to the midaxillary line there was a diastolic sound which seemed nearer the first than the second cardiac sound. The abdomen was scaphoid. The edge of the liver was felt two fingerbreadths below the costal margin, but the spleen was not palpable. The physical examination was otherwise essentially negative.

Laboratory Data.—The blood Kahn reaction was negative. The blood group was 0. The examination of the urine was negative with the exception of an occasional trace of albumin. Urine urobilinogen was normal. Erythrocytes numbered 1,250,000 per cubic millimeter, and the hemoglobin concentration was 3.5 Gm. per cent. The white blood cell count was 36,000 per cubic millimeter, with 83 per cent polymorphonuclear leucocytes. On smear of the whole blood immediate and widespread sickling of the red blood cells was present. Staphylococci were present in the nose. Nonhemolytic streptococci, hemophilus hemolyticus, and staphylococci were found in the throat. Pneumococci Type III were recovered from the peritoneum of a mouse at autopsy after injection of material from the nose and throat. The streptococcal fibrinolysin test[21, 22] was maximally positive (resistant plasma clot) on the twentieth, thirtieth, thirty-sixth, forty-first, and forty-eighth hospital days. Blood cultures were negative on several occasions (February 20, March 6, April 9, and April 10, 1940). The icterus index was 8.

Course.—It was obvious on admission that the child had sickle-cell anemia, probably a basilar pneumonia, and possibly rheumatic heart disease. Supportive therapy and transfusions were given, and sulfapyridine administration was started. Roentgenographic examination of the chest thirty-six hours after entrance to the hospital showed cardiac enlargement with left auricular and left ventricular preponderance, passive congestion of the lungs, and pneumonic infiltration of both lower lobes. The administration of sulfapyridine was continued for one week without any appreciable effect upon the temperature, which ranged between 37° and 39.5° C. A sulfapyridine blood level of 4.5 mg. per cent was attained. A second x-ray examination of the chest, eight days after admission, showed clearing passive congestion but no evidence of a pneumonic process. An electrocardiogram taken at this time revealed a prolonged P-R interval. The child continued to receive supportive therapy and transfusions. One month after admission the diastolic sound at the apex had become a fairly well-defined murmur. Because of this, especially in the presence of the repeatedly positive fibrinolysin test, it was felt even more strongly that the child had active rheumatic fever with carditis. It was also believed that, if the anemia could be corrected, the cardiac enlargement would decrease if it were

due solely to the low hemoglobin and red blood cell count which continued despite seven transfusions. Accordingly, the boy received six more transfusions, a total of thirteen. No one of these exceeded 300 c.c. of blood. The erythrocyte count was elevated to 5,030,000 per cubic millimeter, and the hemoglobin to 13 Gm. per cent.

On the fiftieth hospital day the boy complained of headache and seemed to have a new respiratory infection. His temperature was 39.3° C.; the lung fields were clear; and there was no change in the cardiac status. Nose culture showed pneumococcus Type XVIII and a few colonies of beta-hemolytic streptococci. A transfusion of 250 c.c. of citrated whole blood was given at 8 P.M. that evening; there was no immediate reaction, and the following morning the patient seemed better. However, at 4 P.M. the nurse heard him cry out and on examination found the boy unconscious. The intern found signs of pulmonary edema and a blood pressure of 140 systolic and 100 diastolic. The patient's temperature rose to 42.5° C., and he had clonic spasms of all extremities. He was given morphine, atrophine, and 50 per cent glucose intravenously and was put in an oxygen tent. Three hours later venesection was done, with no apparent relief. The patient went downhill rapidly and died one hour later, four hours from onset of the ictus. Blood taken early in the course of the final episode showed nonprotein nitrogen concentration of 66 mg. per cent.

The clinical diagnosis at his death was: (1) sickle-cell anemia; (2) rheumatic heart disease, active, with mitral stenosis and insufficiency; (3) left ventricular failure with pulmonary edema; (4) cerebral hemorrhage, etiology unknown.

NECROPSY FINDINGS

The anatomic diagnosis was: (A) chronic and acute mitral and tricuspid valvulitis, chronic left atrial endocarditis, rheumatic myocarditis, cardiac hypertrophy and dilatation, congestion and edema of lungs and spleen, massive hemorrhage in basal ganglia with extension to ventricular system; (B) hyperplasia of bone marrow, fibrosis of spleen (clinically, sickle-cell anemia).

Autopsy examination was undertaken two hours after death. The body was that of a poorly developed and inadequately nourished young negro male. The nail beds of the fingers were markedly cyanotic. Inspection of the body cavities revealed their lining to be smooth and glistening.

Removal of the calvarium disclosed the cerebral dura to be stretched as tightly as a drum head. There was extensive symmetrical, gyral flattening and an obvious cerebellar pressure cone. A massive extravasation of fresh blood filled the cisternae magna, pontis, interpeduncularis, and chiasmatis, and spread up over the surface of the cerebellar vermis and hemispheres. Smaller, flame-shaped hemorrhages discolored the leptomeninges of the cerebrum. Section of the brain in a frontal plane revealed a recent intracerebral hemorrhage of tremendous size to have replaced most of the right lenticular nucleus and to have penetrated the internal capsule to empty into the ventricles (Fig. 1). The latter were filled with clotted blood. In its broadest extent the hemorrhage measured 6 cm. by 4.5 cm. Tiny areas of encephalomalacia were present in the subcortex of the right frontal lobe and in the homolateral caudate nucleus. The left internal capsule was intact. There were no aneurysms on the vessels forming the circle of Willis or their ramifications within the cerebral parenchyma. It was impossible to discern the exact source of the apoplexy.

Patches of ganglion-cellular necrobiosis were numerous in histologic preparations of representative sections of the cerebral cortex (Fig. 2). These were chiefly superficial in location, involving laminae I to III in most instances. Several, however, destroyed the whole thickness of the grey matter. Most were perivascular, surrounding small vessels of the precapillary or capillary varieties. The proliferation of astrocytes and of endothelial-lined channels replaced the absent neurones in

many places, and Hortega cells of the "Stäbchenzellen" or "Gitterzellen" types were intermingled with the new vessels and astroglia. Zones in which neurones were present but were pale to the point of virtual obscurity were found elsewhere in the cortex. Dilatation of the Virchow-Robin spaces was encountered frequently in the

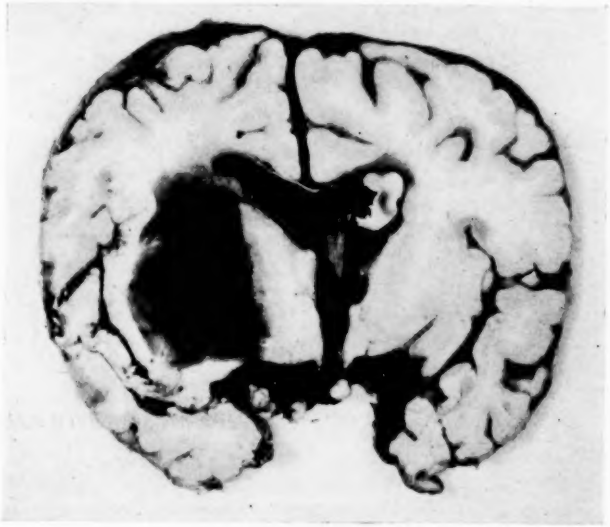

Fig. 1.—Massive hemorrhage in right basal ganglia with penetration into the ventricular system. Clotted blood fills the latter and is present in the arachnoid cisterns.

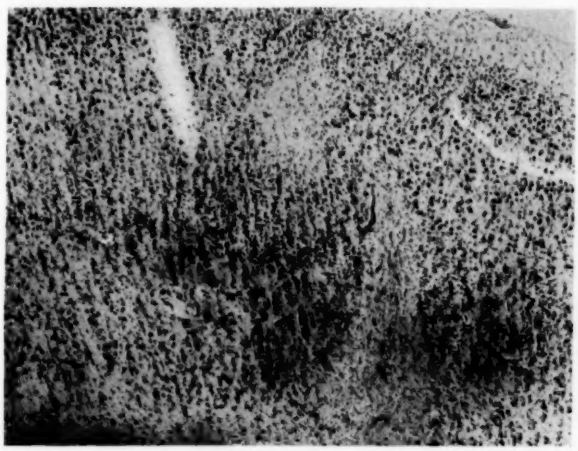

Fig. 2.—Focal areas of ganglion cell loss in cerebral cortex. (Nissl stain, ×50.)

subcortical white matter. Not unusually this had progressed to actual encephalomalacia, the last change being especially prominent in the basal ganglia of the right hemisphere (Fig. 3). Here the enlarged lacunae contained phagocytic mononuclear cells bearing green iron pigment, and pink, "colloid-like" material. A few of the

small vessels of the magnitude of arterioles or venules in the pia and parenchyma had walls which were increased in cellularity and width. One such vascular channel in the right striate body was particularly obvious by reason of hyperplasia of the media. No thromboses were found anywhere. Masses of freshly extravasated erythrocytes, many of them sickled, were present in the meshes of the arachnoid, which was not fibrosed.

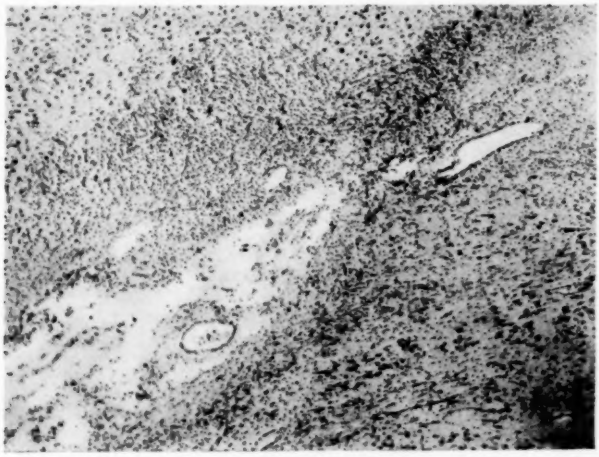

Fig. 3.—Perivascular encephalomalacia in right lenticular nucleus. (Nissl stain, ×175.)

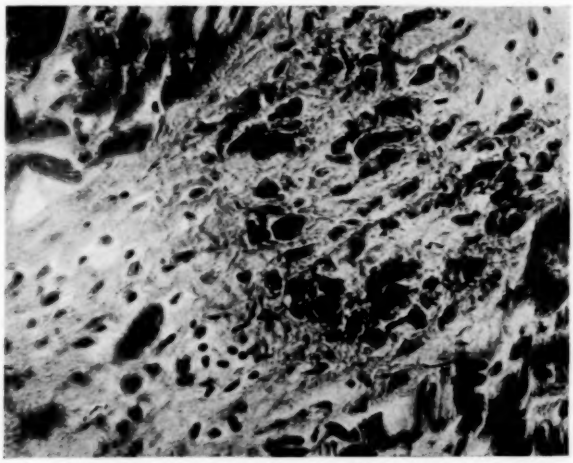

Fig. 4.—Aschoff body in myocardium. (Hematoxylin-eosin stain, ×375.)

The heart weighed 320 Gm. A fibrinous exudate dulled the anterior surface of the left ventricle. The leaflets of the tricuspid and mitral valves were edematous and thickened, and fresh verrucae as well as subendocardial hemorrhages beaded their lines of closure. The internal aspect of the left atrium was yellow-white, opaque,

and puckered in a radial fashion. The myocardium of each ventricle was much hypertrophied and ruddy brown in color throughout. Microscopically, the lesions in the heart were those typical of acute rheumatic fever. They consisted in areas of focal necrosis in which lay club-shaped and twisted, basophilic Aschoff cells, with bizarre, sometimes reduplicated nuclei (Fig. 4). Polymorphonuclear leucocytes and plasma cells as well as occasional eosinophiles infiltrated the tissues adjacent to these Aschoff bodies. The tricuspid and mitral valves were the seat of an acute as well as a chronic inflammatory process. Subintimal fibrosis thickened several coronary vessels, in the walls of which were seen abnormal cellular elements.

Each lung weighed 350 Gm. and was firm and rubbery in consistency throughout. The alveoli were found to be distended with pink, "colloid-like" material, and there was some increase in the fibrous connective tissue of the interlobular septa. The spleen was enlarged, and microscopically the sinusoids of the organ were clearly visible; golden-brown pigment was scattered in the fibrosed interstitium; and the germinal centers of the lymphoid follicles were small or entirely absent. Capillary hyperemia and "sinus-catarrh" were noted in the lymph nodes surrounding the pancreas. There was extreme dilatation and edema of the sinusoids of the liver. Granules of hemosiderin filled the cytoplasm of the epithelial cells forming many of the convoluted tubules of the kidney, and occasionally these cells were necrotic. The glomeruli, arterioles, and pelvis were perfectly preserved. The bone marrow was characterized by an erythroid hyperplasia, early and late erythroblasts as well as normoblasts being especially numerous, with the number of myeloblasts and myelocytes in marked abeyance. Slipper and sickle forms of red cells were present in the sinusoids.

DISCUSSION

Speculation before autopsy concerning the possibility of complicating acute rheumatic fever was referred to above. Mention was also made of the difficulty experienced elsewhere in determining whether an individual was suffering from sickle-cell anemia alone, or sickle-cell anemia complicated by organic heart disease, and the striking similarity of symptoms was stressed.[1-5]

It would seem important to point out, therefore, the result of the fibrinolysin test. The persistently positive test in this patient seemed strong evidence during life for the coexistence of active rheumatic fever. Boisvert has emphasized the frequency of positive tests in children with rheumatic fever. In his experience in this clinic the association of positive tests with rheumatic fever has been striking and has indicated that the test is of diagnostic value.[23] It should be mentioned that the fibrinolysin test has been negative in four patients with sickle-cell anemia[24] followed in the children's clinic.

The specific etiology of the massive cerebral hemorrhage is unknown. Certainly there was no evidence of generalized vascular disease, and the cerebral vessels, large and small, were well preserved. The areas of softening noted in the parenchyma may be of significance in light of the hypothesis as to the pathogenesis of intracerebral bleeding suggested by Globus and Strauss.[25] These workers believed that otherwise unaltered vascular channels may rupture if the supporting brain tissue becomes necrotic. In this connection it would also seem desirable to mention again the repeated transfusions which the patient received.

They were employed for two reasons: (1) to attempt to correct the patient's anemia, and (2) to see if the cardiac status would be altered once the anemia was corrected, for it was felt that, if the murmurs were due to the dilatation of the heart because of the anemia, they would tend to disappear once that anemia was corrected. The amounts of blood given, the erythrocyte counts, the hemoglobin concentrations, and the dates of the transfusions are shown in Table I. It is impossible to state what effect these frequent transfusions had in regard to the sudden death of the patient, but the possibility that there may have been some connection seems to deserve consideration.

TABLE I

DATE (1940)	AMOUNT OF TRANSFUSION (C.C.)	ERYTHROCYTE COUNT (MILLION)	HEMOGLOBIN CONCENTRATION (GM. %)
Feb. 19		1.25	3.7
Feb. 20	300		
Feb. 22	250		
Feb. 22	250		
Feb. 24		2.33	7.5
March 3	250		
March 4	250		
March 5		2.42	7.5
March 14	300		
March 15	250		
March 18		3.40	9.0
March 27	250		
March 28	250		
March 29		3.08	8.5
March 30	200		
March 31	200		
April 1		3.39	10.0
April 6	230		
April 7	270		
April 8	250	4.68	11.0
April 9	250		
April 10		5.03	13.0

The reason for the presence of focal areas of ganglion cell loss in the grey matter of the brain is equally obscure; as stated above, none of the vessels examined were occluded by thrombi or mural change. Transient obstruction to the blood stream by conglutinated masses of sickled or sickling erythrocytes and consequent parenchymal ischemia may have occurred during life.

SUMMARY

A case of sickle-cell anemia and acute rheumatic fever with carditis occurring simultaneously in a negro boy of 12 years is presented. The general necropsy findings were those typical of the two pathologic processes. Death was caused by a massive intracerebral hemorrhage, and associated evidences of chronic cerebral affection were present. The similarity in the clinical pictures of the two diseases is referred to, with special mention of the value of the fibrinolysin reaction as an aid in the diagnosis of rheumatic fever.

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SERUM PHOSPHATASE IN INFANTILE SCURVY

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THE present study is concerned with the low concentration of serum phosphatase observed in infantile scurvy and the rise in the concentration that follows vitamin C therapy.

There are relatively few reports concerning the clinical conditions encountered in infancy which are associated with low serum phosphatase activity. Bodansky and Jaffe[1] state that malnutrition and anemia lower the plasma phosphatase. Roberts,[2] on the other hand, found an increase in phosphatase in most of the cases of anemia he studied. Talbot[3] demonstrated that the serum phosphatase in untreated hypothyroid children tends to be abnormally low (average 3.0 Bodansky units) and that adequate thyroid therapy restores the phosphatase level to normal (average 8.5 Bodansky units). Smith and Maizels[4] studied six cases of infantile scurvy and found figures at the lower limits of the normal range in the acute stage. In one case, that of a 9-month-old infant with subperiosteal hemorrhage, a rise in the phosphatase from 0.15 Kay units to 0.52 Kay units appeared coincident with the onset of calcification of the hemorrhages in a period of two weeks and returned to a normal level of 0.25 Kay units six months later when the bone contour was almost normal roentgenologically. Later, Smith[5] reported phosphatase values in conditions characterized by cessation of growth in fifteen infants ranging in age from 2 months to 2.5 years. This group considered collectively (eight cases of scurvy, three of marasmus, two of celiac disease, one of achondroplasia, and one of cretinism) had an average blood phosphatase of 0.143 Kay units with a range of 0.108 to 0.192 Kay units. The normal range in a group of twenty-three infants under 1 year of age reported by Smith was 0.20 to 0.36 with a mean value of 0.27 Kay units. Todhunter and Brewer[6] induced scurvy in guinea pigs and noted a slight increase in phosphatase activity in mild scurvy (which they felt was statistically insignificant) and a sharp reduction to about one-third the original level in marked scurvy. In unpublished studies Gould and Shwachman found a marked lowering in the serum phosphatase in scorbutic guinea pigs and showed that the administration of vitamin C to these animals will bring about a rapid rise of the serum phosphatase.

Table I presents the serum phosphatase values in eighteen cases of unequivocal scurvy* admitted to The Infants' and The Children's Hospitals from June, 1937, to March, 1941.

From the Infants' and the Children's Hospitals and the Department of Pediatrics, Harvard Medical School.

*In addition to the typical physical signs, symptoms, and characteristic roentgenograms present in all cases, laboratory data of a confirmatory nature were frequently obtained. This included fasting plasma vitamin C levels, absorption tests with urinary excretion studies, and occasional vitamin C studies on the white blood cell fraction.[7]

Bodansky and Jaffe[1] give a mean value of 7.5 Bodansky units for normal children with a range from 5 to 14 units. Barnes and Munks[8] in an extensive study of the serum phosphatase in infancy found a mean value between 11 and 12 Bodansky units at 1 year of age. Expressing the phosphatase activity in terms of Kay units the mean value for normal children as determined by Kay[9] is 0.26 units (range 0.17 to 0.34) and 0.15 units (range 0.10 to 0.21) for adults. The mean value for normal infants and children as determined in our laboratory is approximately 7.2 with a range from 4.5 to 12.0 Bodansky units.[10] The determinations were carried out according to a modification of the Bodansky[11] method by Butler.*

TABLE I

SERUM PHOSPHATASE IN SCURVY

CASE NO.	AGE (MONTHS)	PHOSPHATASE (BODANSKY UNITS)	APPROXIMATE DURATION OF PRESENT ILLNESS (WEEKS)
1	7	4.7	2-4
2	7	1.4	8
3	7	4.7	3
4	8	3.4	1
5	8	3.3	4
6	8	1.3	2
7	8	3.6	3
8	9	2.6	? indefinite
9	9	4.1	3
10	9	2.5	2
11	10	2.8	2
12	10	4.6	4
13	10	2.0	3
14	11	1.1	8
15	11	3.2	2
16	12	3.2	3
17	12	4.6	5
18	13	4.9	16

Most of the initial determinations were made within twenty-four hours after admission to the hospital. In only a few instances was the initial determination made after the institution of vitamin C therapy. The calcium and phosphorus values are not reported as they were not significantly altered. We had an opportunity to study the serum phosphatase following the institution of vitamin C therapy in seven patients. This is illustrated in Table II. It is important to note that vitamin D therapy was withheld in many of the patients during the period of study. A definite rise in phosphatase activity was demonstrable in a period of about one week in most instances. Case 14 is the only one in the entire

*The method consists of incubating 0.5 c.c. of serum with 5 c.c. of a solution containing 0.5 per cent of sodium glycerophosphate (E. K. Co.) and 0.42 per cent of monosodium diethyl barbiturate (Merck) at 37° C. for one hour. The mixture is then cooled in ice water and 4.5 c.c. of a 10 per cent trichloracetic acid solution is added. The precipitated proteins are filtered off, using Whatman filter paper No. 42, and the total inorganic phosphorus is determined in 1.0 c.c. of the filtrate made up to 10 c.c. as follows: 1.0 c.c. filtrate; 7.6 c.c. distilled water; 1 c.c. of 2.5 per cent ammonium molybdate in 5 N sulfuric acid; and 0.4 c.c. of 0.25 per cent aminonaphtholsulfonic acid reagent (Folin's manual, ed. 5, 1934, p. 175). At the end of fifteen minutes the blue color developed is measured in the Evelyn photoelectric colorimeter, using filter 660 with the blank solution set at 100 on the galvanometer scale. The result is read from a calibrated curve.

series with extensive subperiosteal hemorrhages, and in this instance the phosphatase rise was greatest.

TABLE II

RESPONSE OF SERUM PHOSPHATASE IN HEALING SCURVY

CASE NO.	AGE (MONTHS)	DAYS AFTER INSTITUTION OF VITAMIN C THERAPY	SERUM PHOSPHATASE (BODANSKY UNITS)	VITAMIN C ADMINISTRATION PRIOR TO DETERMINATION OF SERUM PHOSPHATASE (MG.)
6*	8	2	1.3	600
		8	5.1	1,800
7*	8	0	3.6	0
		6	3.8	750
		18	10.8	2,550
		29	9.2	4,200
3*	7	0	4.7	0
		10	10.8	3,400
14†	11	1	1.1	200
		10	19.0	2,000
		27	11.8	4,300
15‡	11	0	3.2	0
		7	8.0	950
17*	12	1	4.6	150
		6	13.9	1,050
		15	18.3	2,150
		27	10.6	2,625
18‡	13	0	4.9	0
		8	4.6	1,100

*Vitamin D withheld during period of observation.
†Drisdol (8 Gtt.) begun on fourteenth day.
‡Patient received 10 Gtt. of oleum percomorpheum daily.

DISCUSSION

Evidence from the literature[12] and our own studies[13] suggests that bone is the major source of serum phosphatase and that this enzyme may serve as an index of osteoblastic activity.[14, 15] The observation of increased serum phosphatase in active rickets is consistent with a picture of overactivity of the osteoblastic tissue. In scurvy, on the other hand, the pathologic picture is one of inactivity or inability of the osteoblasts to form bone matrix. It is not surprising then, that this state of affairs is reflected in the lowered activity of serum phosphatase. Likewise in hypothyroidism where there is an arrest of bone growth and activity the serum phosphatase is reduced.[10]

The administration of vitamin C in scurvy institutes morphologic changes in the osteoblastic tissue indicative of recovery in a surprisingly short period, as demonstrated by Wolbach and Howe.[16] This healing process is reflected in a rise of the serum phosphatase and may be observed as early as one week after the institution of vitamin C therapy. Normal children show no change in serum phosphatase activity following administration of large doses of ascorbic acid. In one instance (Case 15) (Table II) the rise in phosphatase was detected when less than 1 Gm. of ascorbic acid was given. Why the rise in two instances (Cases 14 and 17) exceeded the upper limits of normal is not entirely

clear. Case 15 deserves comment because there was no rise following vitamin C administration. On entry the plasma phosphatase level was 4.9 Bodansky units, the highest in the series. This infant was the oldest in the series (13 months) and also had symptoms extending over the longest period (four months). The roentgenograms on admission revealed a long-standing scurvy in the course of which sufficient healing had taken place to allow calcification of hemorrhages at the distal ends of the femora. This may explain the failure of the serum phosphatase to rise as in the preceding six cases. It is apparent that the rise of phosphatase with initial healing is not solely dependent upon the presence of subperiosteal hemorrhages undergoing calcification. Although the rise was greatest in the case with extensive subperiosteal hemorrhage, there was a definite rise in five of the other cases without demonstrable hemorrhage. Smith and Maizels[4] felt that the calcifying blood clot contributed materially in increasing the enzyme activity and left the problem open concerning the response when such hemorrhage did not occur.

A situation often difficult to appraise is the presence of both rickets and scurvy, in varying degrees, in the same infant. It may be well to recall that the elevation of the serum phosphatase may be the very first sign of rickets and that healing brings about a decline to a normal level. When a normal or high phosphatase value is obtained in an infant with acute scurvy, the presence of some complicating condition such as rickets should be suspected.

CONCLUSION

1. The serum phosphatase is abnormally low in acute scurvy in infancy. The average value of eighteen cases upon admission to the hospital was 3.2 Bodansky units with a range of 1.1 to 4.9 units, as compared with the mean value for normal infants of approximately 7.2 with a range from 4.5 to 12 units.

2. There is a substantial rise in serum phosphatase in infantile scurvy within approximately one week following the institution of vitamin C therapy.

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THE PATHOLOGY OF MUMPS ENCEPHALITIS

With Report of a Fatal Case

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INVOLVEMENT of the nervous system in mumps is not uncommon and may be manifested in a variety of ways. The most common is the so-called meningitis or meningoencephalitis which results in an infiltration of cellular elements, chiefly lymphocytes, into the spinal fluid. This pleocytosis of the cerebrospinal fluid may or may not be accompanied by symptoms of meningeal irritation. Latent encephalitis of mumps is a unique phenomenon in which there is a mild or a pronounced infiltration of cells, chiefly lymphocytes, into the cerebrospinal fluid as disclosed by a routine lumbar puncture without there being any symptoms or outward signs whatever, to suggest meningeal irritation.

Other less common neurological manifestations of mumps which have been described are myelitis, polyneuritis, and neuritis limited to one or more nerves such as facial, trigeminal, auditory, and optic. Although some of these may result in permanent damage, more frequently the paralysis is transient. The various neurological complications of mumps have been reviewed by McKaig and Woltman[1] and Wesselhoeft.[2]

The frequency with which encephalitis develops in mumps as cited by various investigators varies widely, from 0 to 40 per cent (Wesselhoeft,[2] Finkelstein[3]). None of these figures represents a true incidence, as many are observations made in military institutions and give only the adult male incidence during an epidemic. The figures, also, depend upon the thoroughness of the investigation, for, unless routine lumbar punctures were carried out, many cases of latent encephalitis would be missed. Since mumps is largely a benign disease of childhood and treated at home, those cases which enter hospitals are usually severe or have already developed complications. Thus statistics obtained from hospitals are misleading. As a rule, the more carefully this particular manifestation is looked for, the more frequently it is found. There appears, also, to be considerable variation in the incidence of nervous system involvement during different epidemics.

Fortunately, in spite of the frequent involvement of the nervous system in mumps, complete and uneventful recovery is the rule. Reports of fatalities in the literature are uncommon, and even rarer are accounts in which a histologic study of the central nervous system has been made in those cases which came to post mortem. For this reason the changes which take place in the central nervous system have not been satisfactorily established.

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De Lavergne, Kissel, and Accoyer (1937)[4] reviewed the literature and found reports of only twelve patients with mumps who had died as a result of neurological complications. In only four of these had a microscopic examination of the nervous system been made. These authors did not include the four somewhat doubtful cases of Gordon,[5] nor the case reported by Larkin.[6] Since this review there has been one additional case described by Urechia[7] in which a postmortem examination was made. A brief review of the reports of various authors dealing with the microscopic changes in the central nervous system in patients dying as a result of neurological complications associated with mumps will demonstrate the wide diversity of pathologic lesions encountered and the paucity of the data concerning the changes which occur in mumps encephalitis.

Barnes (1902)[8] described a case of a woman of 34 years who developed a quadriplegia following mumps. This was followed by persistent atrophy of the hands and feet. She died more than a year later of another cause. The anterior horn cells of the cervical and lumbar enlargements showed marked atrophy and degeneration. The corresponding peripheral nerves showed degeneration of their axis cylinders and disappearance of myelin. Although this case was included in the series reported by de Lavergne and his associates, it is doubtful if the neurological picture which developed in this case had any etiological relation to mumps.

Bien (1913)[9] reported the case of a boy of 8 years who, eight days after an attack of parotitis, developed convulsions and died in coma twenty-four hours later. In this case there was infiltration of the perivascular spaces with compound granular corpuscles and perivascular areas of demyelinization in the white matter.

Gordon (1913)[5] published a report of four cases. These are important and well reported. There are three boys and a girl, aged 2 years, 2 years 10 months, 5 years, and 9 years. In none of the cases was mumps diagnosed clinically. In one case the parotids were found to be slightly enlarged. All cases showed clinically signs of central nervous system involvement. In two there was an increased number of cells in the cerebrospinal fluid. At post-mortem examination all showed an interstitial infiltration with lymphocytes in the parotid gland. Although the reproductions of the photomicrographs are not clear, the lesions appear to be similar to those seen in the case encountered by the author. The findings described in the central nervous system were not striking nor did they have any definite characteristics. They consisted of slight and varying meningeal infiltration, congestion, and some increase in glial cells. Wasting and chromatolysis were found in a few anterior horn cells. In one case there was a perivascular infiltration with lymphocytes in one section. Unfortunately, there were no photomicrographs of the lesions in the central nervous system. As all these cases occurred during an epidemic of mumps and as the lesions in the parotid were

compatible with those of mumps, it seems quite possible that these were true cases of mumps meningoencephalitis, although they are considered doubtful by most investigators.

Larkin (1919)[6] reported a case of a male, white, aged 31 years (claimed to have had mumps 3 years previously) who was admitted to the hospital with clinically typical bilateral mumps. He showed evidence of cerebral involvement three days after admission. Lumbar puncture showed 300 cells, 30 per cent polymorphs, and 60 per cent lymphocytes. The patient grew worse rapidly and died seven days after admission, four days after the onset of cerebral symptoms. The brain showed an extensive accumulation of slightly turbid fluid in the cisterna magna. The pia arachnoid was congested. In many places a perivascular exudate was seen in the form of greyish yellow lines following the course of the blood vessels. The ventricles were somewhat distended. The fluid was clear. The ependyma was slightly granular. Cultures (aerobic) from the perivascular exudate and from the spinal fluid were negative. "Microscopic sections showed the pia arachnoid to be densely infiltrated with large and small mononuclear cells. The infiltrations were definitely perivascular but also extended into the areolar tissue and the cortex. Similar cells were adherent to the arterial intima."

Wegelin's (1935)[10] report concerns a boy of 8 years who, eleven days after parotid and submaxillary mumps, developed signs of meningoencephalitis. The child died in convulsions after three days. The meninges were infiltrated with lymphocytes. The blood vessels of the meninges were congested and surrounded by thick mantles of lymphocytes. The choroid plexus was congested. In the central nervous system there were numerous perivascular hemorrhages. Many of the blood vessels were surrounded by mantles of inflammatory cells, chiefly lymphocytes and swollen adventitial cells. In some places this infiltration was limited to the perivascular space. In other places it extended into the surrounding parenchyma and merged with foci of neuroglial reaction. This neuroglial reaction was, for the most part, perivascular in distribution, but sometimes it had no apparent relationship with blood vessels. These foci were associated with some demyelinization.

Cathala, Bertrand, Bolgert, and Auzépy (1936)[11] described the case of a man of 38 years who, eight days after a parotitis and five days after an orchitis, developed a diffuse and progressive quadriplegia. He died nine days later of bulbar involvement. In this case practically no changes were found in the brain and cord, and it was presumed that the lesions must have occurred in the peripheral nerves. Unfortunately, these were not examined.

Urechia (1938)[7] reported the case of a 54-year-old woman who was admitted with an acute psychosis of three days' duration. The patient became progressively worse and died six days after admission. There was no lumbar puncture. In the clinical report no mention of mumps was made until two days before death when it was merely stated that

bilateral parotitis was confirmed. The central nervous system showed irregular thickening of the meninges, congestion of the vessels, and small hemorrhages both recent and old. In some places there was phagocytosis of blood pigment. The endothelium of the blood vessels was swollen. There was perivascular infiltration with lymphocytes. In the brain tissue itself there were congestion and perivascular infiltration. In the adventitia of some of the vessels there were deposits of fat. In the myelin nothing significant was found. Urechia interpreted these changes as those of a resolving meningoencephalitis from which the patient probably would have recovered if she had not died of a myocarditis. From the clinical history and the microscopic report there may be some doubt as to whether this is a true case of mumps encephalitis. The presence of phagocyted blood pigment would indicate a lesion of some duration, possibly vascular in origin.

In attempting to determine a pattern for the histopathologic changes in the encephalitis of mumps, one is limited to the above ten cases in which a histologic study of the central nervous system had been made. In a consideration of encephalitis alone, two of the cases need not be considered because in both the picture was that of a myelitis rather than an encephalitis; in one (Cathala and his co-workers)[11] no lesions were found in the central nervous system; in the other (Barnes)[8] besides being of doubtful etiology the microscopic examination was made after an interval of over a year after the onset of symptoms, and the resulting picture was merely the end result of a process which had long since reached its termination. If one considers the remaining eight cases, including five which are doubtful (i.e., four of Gordon's[5] and that of Urechia[7]), the picture is somewhat varied. The brain and cord may show only congestion. Meningeal infiltration may vary from a few lymphocytes to gross exudate. Petechiae and perivascular hemorrhages are described. Perivascular infiltration with lymphocytes and compound granular corpuscles, either limited to the perivascular space or extending into the surrounding parenchyma, occur. Perivascular demyelinization with neuroglial reaction may be present. Even if the doubtful cases are excluded and only those of Larkin,[6] Bien,[9] and Wegelin[10] are considered, the histologic picture is still varied in type and severity. The meningeal exudate described by Larkin is much more abundant than that described by Bien and Wegelin. Larkin apparently did not examine the tissue for changes in the myelin.

CASE REPORT

J. K. was a 5-year-old girl. Eleven days previous to admission the mother noticed that the child had sniffles and a dry cough. Three days later the child's face became swollen in the left parotid region. This gradually increased and became painful. Two days later the right side of the face was similarly affected. During this time the child had been up and around, and a doctor had not been consulted. Five days after the onset of the original parotid swelling and three days previous to admission the bilateral parotid swellings had almost completely subsided.

Nothing unusual was noted until approximately thirty hours prior to admission when the mother noticed that the child appeared to be unable to see where she was going. An hour or so later she had several chills over a period of about two hours. She seemed stuporous and dazed. Weakness of the legs developed. During the night previous to admission the child wakened repeatedly screaming.

On admission the child was dazed, irrational, and obviously acutely ill. Temperature was 102° F.; pulse, 120; respiration rate, 28. Aside from the nervous system the physical examination was essentially negative. The patient was irrational, disorientated, and apparently could not speak. As far as could be ascertained the cranial nerves were normal except for a right internal strabismus. All limbs appeared slightly hypertonic. Voluntary power was untestable but appeared normal when the child involuntarily resisted movement. She reacted to pinprick over her entire body. Reflexes were normal but hyperactive. Kernig's and Babinski's signs were positive. The cerebrospinal fluid showed a slightly increased pressure, was clear, and contained forty-five cells per cubic millimeter, approximately 90 per cent lymphocytes. It was sterile on culture. Blood Wassermann and tuberculin tests were negative.

Progress.—For the first twenty-four hours the child seemed somewhat improved but remained unconscious. Subsequently she grew worse rapidly and died three days after admission with evidence of pulmonary involvement.

Autopsy Report.—The post-mortem examination was performed two hours after death. Only the positive findings will be mentioned. There was a patchy consolidation of both lungs. Both parotid and submaxillary glands appeared grossly normal and were not enlarged or congested although there were a few enlarged and firm lymph glands in their immediate neighborhood. The brain and cord showed a diffuse pinkish blush and a moderate congestion of the superficial vessels. There was no gross evidence of exudate. After fixation in formalin the cut surface of the brain and various levels of the cord showed a slight congestion of the blood vessels. Around some of the vessels in the white matter of the cerebrum and cerebellum there was a narrow, ill-defined, pale yellowish discoloration.

Microscopic Examination.—Lungs: There were patchy and confluent areas of typical bronchopneumonia. Pancreas was normal. Ovary: The tissue was congested, and there were several small follicular cysts. In one of these there was a scanty exudate of mononuclears and polymorphs. However, there was no inflammatory infiltration in the stroma. These changes could possibly be interpreted as a mild oophoritis. Parotid and submaxillary glands: Both these tissues presented essentially the same changes. The changes were somewhat more marked in the parotid than in the submaxillary. There was an extensive interstitial infiltration with lymphocytes and mononuclears (Fig. 1). This was most marked about the ducts, many of which were distended with plugs of inspissated secretion and contained, in addition, a few polymorphs. The epithelium lining the ducts, although somewhat flattened, was intact. The infiltration had resulted in some compression of the ascinic tissue, but this tissue did not appear to be extensively involved. Laidlaw's method and a modified Mann's method of staining showed no inclusion bodies. Brain and cord: There was a slight diffuse infiltration of the meninges of the brain and cord with lymphocytes and a few mononuclears. The vessels were moderately congested. The characteristic lesion throughout the parenchyma of the central nervous system was essentially a perivascular demyelinization with attendant reaction on the part of the glial and mesodermal tissues (Figs. 2 and 3). These changes were found in the white matter of the cerebral hemispheres, the cortex and the basal nuclei being spared, in the white matter of the cerebellum, including the dentate nucleus, in the midbrain, the pons, the medulla, and the cord. The lesions in the cord were severe in the cervical region but decreased in severity at lower levels (Fig. 4). In the lumbar region there was only a slight suggestion of perivascular infiltration. The changes in the cord were most marked in the grey

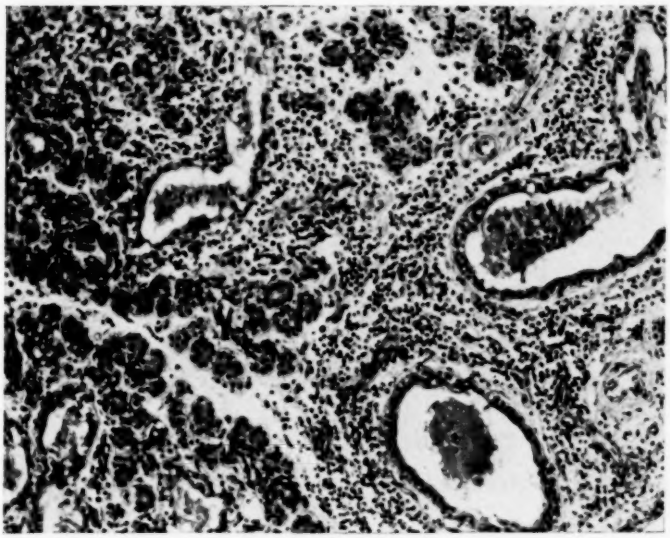

Fig. 1.—Parotid gland. Nonsuppurative interstitial inflammation. The ducts are dilated and contain plugs of inspissated secretion. (Paraffin: Hematoxylin and eosin ×120.)

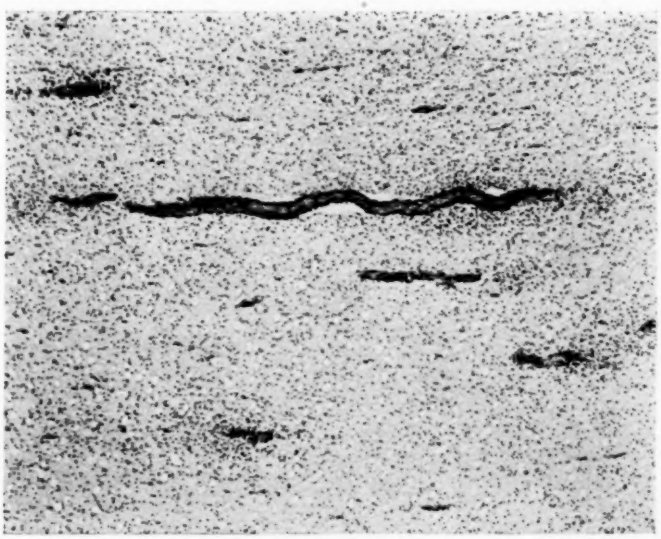

Fig. 2.—White matter of parietal lobe. Perivascular infiltration of rather mild degree. (Pyroxylin: hematoxylin and van Gieson ×50.)

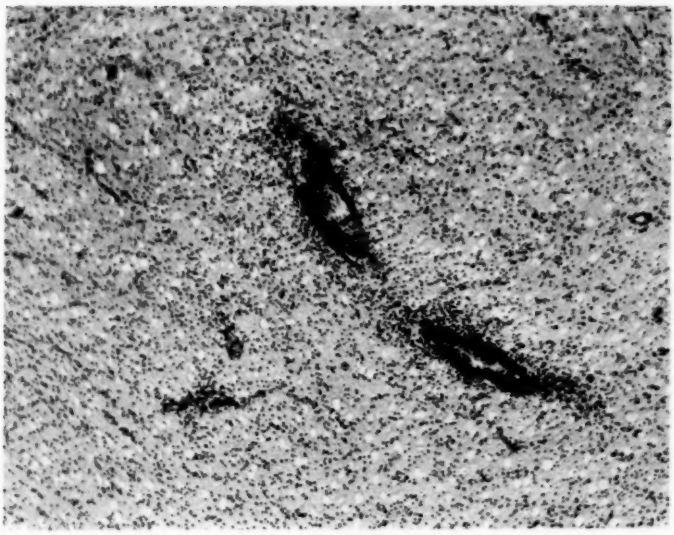

Fig. 3.—Upper part of internal capsule. Characteristic perivascular infiltration. (Pyroxylin: hematoxylin and van Gieson ×50.)

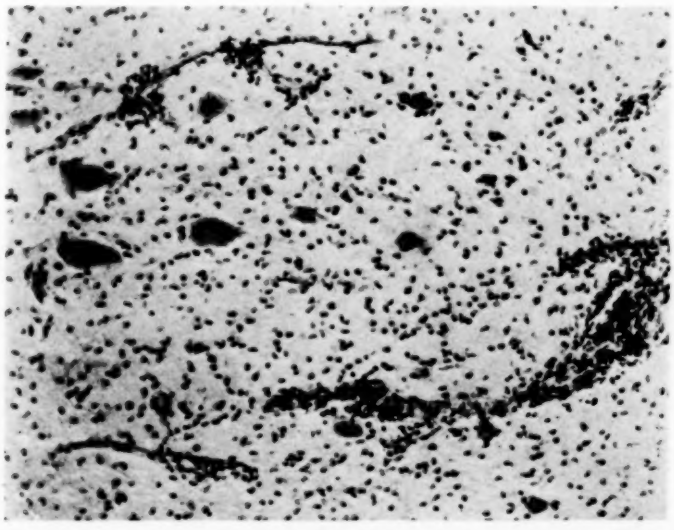

Fig. 4.—Anterior horn of cervical cord. The perivascular reaction is present. The anterior horn cells are well preserved. The apparently degenerating forms are out of focus. (Pyroxylin: hematoxylin and van Gieson ×120.)

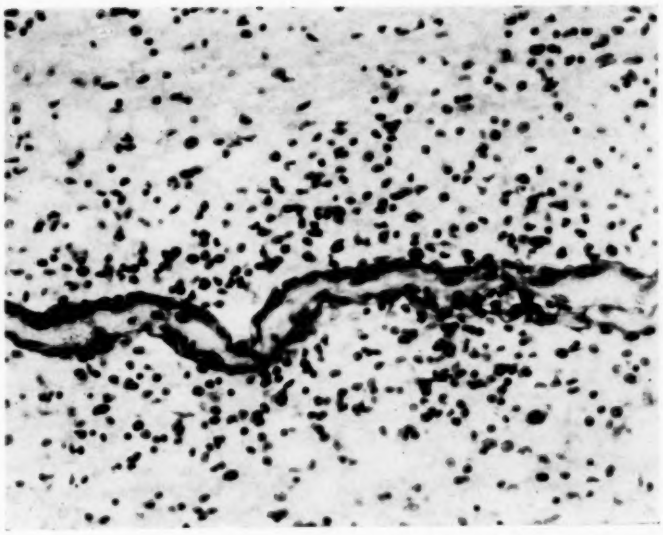

Fig. 5.—White matter of cerebellum. The infiltration is mainly outside the perivascular space. Most of the infiltrating cells are microglia. (Pyroxylin: hematoxylin and van Gieson ×240.)

Fig. 6.—White matter of cerebellum. Perivascular areas of demyelinization. (Pyroxylin: Weigert-Pal ×65.)

matter but were essentially the same as those seen elsewhere and did not primarily involve the nerve cells. In all portions of the brain and cord involved there was a perivascular infiltration with many microglia and some swelling and proliferation of the astrocytes. Although there were a few cells in Virchow-Robin's space, most of the cells were immediately outside this space in the adjacent parenchyma. The main infiltrating cell had a rather darkly staining nucleus of medium size (Fig. 5). Many of these nuclei were irregular in shape. Rod, hooked, and boomerang forms were common. These were interpreted as the nuclei of microglia which were in an active amoeboid phase. The processes of these cells could not be stained with the silver carbonate technique. The infiltration extended out from the blood vessels into the parenchyma decreasing in density and gradually merging with the surrounding normal tissue. This zone of infiltration corresponded to a zone of demyelinization which was shown in preparations stained by the Weigert-Pal method (Fig. 6). This demyelinization was quite characteristic. The myelin sheaths adjacent to the blood vessels showed all stages of degeneration, irregularity, beading, fusiform and globular swellings, and complete disappearance. The perivascular damage to the myelin was not as extensive or severe as frequently seen in other postinfection encephalitides. Scharlach-R stain of the areas showing demyelinization revealed only an occasional cell containing neutral fat. These were present in the perivascular space and adjacent parenchyma.

There was very little evidence of inflammation aside from that occasioned by the degeneration of the myelin. Polymorphonuclears were not encountered. In the grey matter of the cervical cord there were a few small perivascular hemorrhages. This was the only area in which they were found. In grey matter free or practically free of myelin, such as the cerebral cortex, basal nuclei, and cerebellar cortex, there were no demonstrable changes. However, nuclei such as the dentate and inferior olive, which contain a considerable proportion of myelinated fibers, and the grey matter of the cord showed extensive damage. In the various regions involved the nerve cells showed some swelling and chromatolysis but were not primarily affected.

The histologic picture found in this case is quite clear cut, and it falls definitely into the well-recognized group of the so-called postinfection encephalitides or acute perivascular myelinoclasis which may follow such diseases as smallpox, chickenpox, measles, and vaccination.

COMMENT

The histologic picture of mumps encephalitis as described in the few reports in the literature is varied and for the most part follows no set pattern. However, the changes described by Bien and Wegelin are similar to those found in this case. As far as the author is aware, the reports by these two, with the exception of Larkin's case which is described rather superficially in regard to microscopic changes, are the only two in which the histopathologic changes are adequately described and in which there can be no doubt that it is an encephalitis complicating mumps with which they are dealing.

The question which immediately comes to mind is whether or not the few cases of mumps encephalitis which have been fatal are extreme examples of the same process so commonly an accompaniment of mumps and usually benign, or a manifestation of a superadded process. It has been suggested that in the fatal cases we are dealing with an entirely different process. In these instances the mumps virus is probably not responsible for the severe and protracted encephalomyelitis occasionally

encountered. The process is rather the result of an invasion with a secondary agent or a latent virus activated by the mumps virus. This is the view held by Wesselhoeft,[2] and it is substantiated if one accepts the concept that the other postinfection encephalitides are the result of a hidden virus which has been activated by the associated disease.

There are several theories of the etiology of these postinfection encephalitides or acute perivascular myelinoclases:

1. There is an augmentation of the neurotropic properties of the virus of the associated disease.

2. A latent virus is stimulated or activated by the infectious disease. One of the chief arguments in favor of this theory is that there is a marked similarity in the incubation period, the clinical picture, and the pathologic findings in all such cases.

3. Another explanation suggests that the demyelinization is due to the activity of some toxin liberated during the course of the disease.

4. The disease process is the result of a local allergic reaction of the nervous system in which the virus of the associated infectious disease acts as a sensitizing agent.

Against the first three suppositions, according to Fothergill,[12] is the fact that no virus has ever been isolated from the brains of these postinfection encephalitides and that no toxin has been demonstrated. This statement, however, will bear close examination because vaccinia virus was found in the brains of two postvaccinal encephalitides by Turnbull and McIntosh.[13] It might be argued that this would be expected as vaccinia virus is pantropic and, according to Ohtawara,[14] may be found in many tissues and in the blood for some time following vaccination; and it does not necessarily follow that the vaccinia virus obtained from the brain in these cases was the cause of the encephalitis.

However, if facile and definite methods of handling the viruses of the acute infectious diseases occasionally followed by this type of encephalitis were at hand, and if a sufficient number of fatal postinfection encephalitides were adequately investigated, the virus of the attendant disease might be isolated more frequently from the central nervous system.

One might point out as argument against a common factor in these perivascular demyelinating diseases the fact that there are many other forms of encephalitis, such as St. Louis encephalitis and equine encephalomyelitis in man, which we know to be caused by different etiological agents and which we would have great difficulty in differentiating on a purely anatomic basis.

In favor of the first theory in regard to mumps encephalitis is the fact that it is fairly generally assumed that the mumps virus is commonly neurotropic. It seems hardly necessary to postulate an additional factor in fatal cases even though only very rarely does this virus prove lethal.

The lesions in the case presented, although fundamentally identical with those found in the central nervous system of the postinfection encephalitides following other diseases, were not of the same order of severity usually seen in these. If the lesions in this patient with mumps encephalitis had not been so widespread or if pulmonary complications had not been present, it is conceivable that recovery might have taken place.

Unfortunately, no virus studies were undertaken on the tissues obtained from the case reported.

A survey of the post-mortem studies on patients who undoubtedly had encephalitis associated with mumps and on whom adequate histologic studies have been made has revealed changes similar to those found in the case described. It is felt that the findings as presented above are characteristic of fatal mumps encephalitis.

SUMMARY

1. The literature on the histopathology of mumps encephalitis has been briefly reviewed.

2. A case of mumps encephalitis with post-mortem studies has been reported.

3. The fundamental lesion was a perivascular demyelinization similar to that seen in other postinfection encephalitides.

4. The etiology of postinfection encephalitis has been briefly discussed.

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BACILLUS MORGANI, TYPE I, IN ENTEROCOLITIS OF INFANTS

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ENTERIC infections of man may be caused by a large variety of different microorganisms, including *Endamoeba histolytica,* vibrio cholerae, typhoid, paratyphoid, and dysentery bacilli. The number of proved pathogenic enteric microorganisms is constantly increasing. For instance, in addition to the bacillus discovered in 1898 by Shiga, other dysentery bacilli described by Flexner in 1900, by Sonne in 1915, and by Clayton and Warren in 1929 are recognized today as the causative agents of dysentery. The methods for the isolation and identification of these enteric pathogens have been greatly improved. It is important to note, however, that even careful bacteriologic examinations not rarely fail to recover any of the recognized pathogenic microorganisms. Cooper, Furcolow, Mitchell, and Cullen[1] in a thorough bacteriologic study on the occurrence of dysentery bacilli in acute diarrhea of infants and children made the important observation that 75 per cent of patients under 1 year of age did not have dysentery bacilli, while 75 per cent of those over 1 year of age did. Bloch[2] found that nonspecific forms of enteritis occurred most commonly in infants. In a series of 422 cases, 71 per cent were infants of less than 1 year of age. This seems to indicate that organisms other than dysentery bacilli are rather frequently the cause of diarrhea in infants. Three possibilities have to be considered at the present time: (1) Diarrhea, on the basis of enteritis, colitis, or enterocolitis, may be nonbacterial in origin; (2) it may be caused by a virus; or (3) it may be due to other enteric bacteria which today are not generally recognized as enteric pathogens. To the latter group of bacilli belong such organisms as *B. proteus, B. pyocyaneus, B. morgani, B. alkalescens,* atypical varieties of *B. coli,* and others. Some investigators have presented evidence that these organisms in certain instances are the cause of diarrhea, particularly in infants and children, while other authors consider them as nonpathogens. In view of the fact that the pathogenic significance of the Morgan bacillus in enteric diseases is not as yet definitely established, we should like to present the bacteriologic and clinical findings of several cases of enterocolitis from which Morgan bacilli were isolated.

Six of these cases were infants ranging in age from 6 weeks to 7 months. These children were admitted to the Children's Hospital between July 22, 1940, and Aug. 14, 1940. The patients presented the typical features of severe enterocolitis. All of them were severely de-

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hydrated and markedly toxic; they had vomiting and from four to fifteen stools per day. The patients were given glucose solution intravenously, and five of them were transfused from one to six times. In addition, these patients were put on an initial starvation period, followed by the administration of protein-milk. Four of the six patients died, and only two recovered.

A seventh patient with mild enterocolitis from whom Morgan bacillus, Type I, was isolated was admitted to the hospital in March, 1940; he recovered and was discharged after a stay of thirty-seven days. This patient also had otitis media caused by pneumococcus, Type III.

The clinical and pathologic data of these cases are summarized in Table I.

The bacteriologic examination of the feces of these patients was carried out as follows: As soon as the specimens were received, small amounts of the material were streaked on the surface of three different solid culture media, namely, Endo-agar, MacConkey's agar and eosin-methylene blue agar (Difco). The technique used is described in detail since it gives satisfactory results. In order to obtain isolated colonies, a small area (approximately one-third) of each plate was first seeded; then the loop was sterilized and cooled, and material from the first inoculation of the plate was taken up and streaked on another part of the same plate (second-third); material from the second inoculation was then taken up for seeding of the remaining part of the plate. In addition to these solid media, broth containing a small piece of calf's liver was seeded with fecal material and then sealed with vaseline; this liver broth served as anaerobic culture medium. Nonlactose fermenting colonies were fished from the agar plates and identified by further study of their biochemical and antigenic characters. They were tested for motility, for fermentation of dextrose, lactose, sucrose, maltose, mannitol, xylose, and rhamnose, for their capacity to produce indol and to liquefy gelatin, and for their reaction in litmus milk. The fermentation tests (phenol red as indicator) were kept at 37° C. up to three weeks. Inverted fermentation tubes (Dunham) were used with dextrose and mannitol. Since it was found that autoclaving at 15 pounds' pressure caused a partial breakdown of some of the test substances, thus giving false reactions, sterilization of lactose, maltose, rhamnose broths was done by filtration through Seitz filters. Autoclaving does not directly cause a noticeable change of the pH; however, organisms that do not ferment the original substances may cause acid or acid and gas formation by action upon the breakdown products. Such reactions must be carefully avoided.

The most important bacteriologic finding in the above reported cases is the fact that careful examination failed to reveal any of the recognized enteric pathogens such as members of the typhoid, paratyphoid, or dysentery bacillus groups. On the other hand, in all cases but one, Morgan bacillus, Type I, was isolated from the intestinal canal. The patient from whom Morgan bacillus, Type I, was not recovered has been included in this series in view of the following reasons: The child developed acute enterocolitis at the same time as his twin brother; no recognized enteric pathogens could be isolated from this infant; the mother harbored Morgan bacillus, Type I, in the intestinal canal at that time; the organism isolated from the mother was identical with that obtained from the other twin.

TABLE I

MORGAN BACILLUS TYPE I IN ENTEROCOLITIS OF INFANTS

NO.	NAME	AGE	ADMISSION DATE (1940)	STAY AT HOSPITAL (DAYS)	NO. OF STOOLS PER DAY	DEHYDRATION	VOMITING	TRANSFUSIONS	GLUCOSE IV.	OUTCOME	CONCOMITANT DISEASES	POST-MORTEM FINDINGS
1	P. G.	3 months	July 22	17	7-11	+	+	3	+	D	Otitis media (staph.)	Acute pseudomembranous enterocolitis; terminal bronchopneumonia; otitis media
2	D. G.	3 months	July 23	19	4-9	+	+	2	+	D		Acute pseudomembranous enterocolitis; terminal pneumonia
3	P. N.	6 weeks	July 31	10	4-6	+	+	2	+	D		Acute pseudomembranous enterocolitis
4	R. B.	5 months	July 31	4	7-9	+	+	1	+	D		Acute catarrhal enterocolitis
5	D. B.	3 months	July 25	41	4-9	+	+	6	+	R		
6	A. P.	7 months	August 14	16	10-15	+	+	0	+	R		
7	C. W.	3 months	March 31	37	1-3	−	+	0	−	R	Otitis media (pneum. III)	

R, Recovery; D, deceased.

The organism recovered from the cases of our series had the following characters: It was a Gram-negative bacillus which grew readily on artificial culture media, including Endo-agar. It produced acid and small amounts of gas from dextrose within twenty-four to forty-eight hours and failed to produce acid or gas from lactose, maltose, mannitol, sucrose, dulcitol, and rhamnose. It is interesting to note that some of the strains isolated from these patients produced acid and small amounts of gas from xylose, while other strains failed to do so. The organism caused acid production in litmus milk, followed later by a change to the alkaline side. Peptonization or reduction did not occur in litmus milk. The organism did not liquefy gelatine. A suspension of the organism in physiologic saline solution showed marked clumping.

TABLE II

IMPORTANT CHARACTERISTICS OF MORGAN BACILLI

B. MORGANI	MOTILITY	FERMENTATION OF					INDOL FORMATION
		DEXTROSE	LACTOSE	SUCROSE	MANNITOL	DULCITOL	
Type I	+	A G	O	O	O	O	+
Type XIV		A G	O	O	A G	O	
Type XII		A G	O	A G	A G	O	
Type X		A G	O	A G	A G	A G	

O, No acid or gas formation; A G, acid and gas formation.

The biochemical characters of Morgan bacillus, Type I, are rather typical and differ distinctly from all other pathogenic and nonpathogenic enteric bacilli with the possible exception of the Clayton-Warren (Newcastle) dysentery bacillus. The organism isolated from the above described cases of enterocolitis could be readily differentiated from the Newcastle bacillus and identified as Morgan bacillus, Type I, since it was motile, did not produce acid and gas from dulcitol, and formed indol. On the other hand, the other types of Morgan bacilli do not have these distinct biochemical features and may even be confused with members of the paratyphoid group. The more important characters of the different types of Morgan bacilli are presented in Table II, because most textbooks do not furnish the pertinent data on Morgan bacilli Types X, XII, and XIV.

DISCUSSION

There is no doubt that Morgan bacilli are pathogenic for men and cause diseases such as septicemia, cholecystitis, infections of the urinary tract, meningitis, mastoiditis, peritonitis, and other purulent lesions.[3] On the other hand, their pathogenic significance in enteric infections is not as yet fully elucidated. Numerous investigators, including Ohrum and Bahr, Phalen and Kilburen, Lewis, Alexander, Bahr and Ohrum, Archibald, Hadfield, Logan and Campbell, d'Hérelle, Logan, Tribondeau and Fichet, Jungmann and Neisser, Seligman, Rey, Besson and de Lavergne, Dopter, Dick, Dick and Williams and D'Aunoy, described

the occurrence of Morgan bacilli in the stools of children with summer diarrhea and also in patients (both children and adults) with enteritis and with typical or atypical dysentery (Neter and Goodale[3]). Other authors, including Davison,[4] Thjotta,[5] and Gardner,[6] consider the Morgan bacillus not as the primary cause of enteric disease, but rather as a nonpathogenic organism more frequently found in patients with intestinal disturbances. Thus, there is a need for further information in regard to the role played by Morgan bacilli in enteric diseases.

In a thorough study on the normal fecal flora of infants between 2 weeks and 1 year of age, Snyder[7] did not encounter Morgan bacilli. The incidence of this microorganism in patients with diarrhea varies from 1.15 per cent (Wollstein) to 16 per cent (Khaled). Moore, and Dennis,[8] studying children with diarrhea at Beirut, Syria, isolated Morgan bacillus in 4.79 per cent of the cases; their observations seem to support the concept of the pathogenicity of the Morgan bacillus.

The cases presented above showed several interesting features. Six of the cases were infants ranging in age from 6 weeks to 7 months who were admitted to the Children's Hospital within a period of three weeks because of severe acute enterocolitis. Four of the patients died, and only two recovered. The only possibly pathogenic organism that could be isolated from these cases was Morgan bacillus, Type I. The question may be considered whether infants under certain conditions may be more susceptible than older children and adults to an infection with this microorganism which from the point of view of pathogenicity may be classified as an intermediate between the true pathogens of the typhoid, paratyphoid, dysentery bacillus groups and the nonpathogenic organisms which are normally found in the intestinal canal of infants and children.

In regard to the possible source of the infection, no definite statements can be made. However, the mother of two infants (twins) of our series who developed enterocolitis at the same time harbored Morgan bacillus, Type I, in the intestinal canal; on bacteriologic examination the bacillus proved to be identical with that isolated from the patient.

The possibility that, following an attack of enterocolitis, patients may become carriers of Morgan bacillus, Type I, is suggested by a patient of the above series who harbored this organism for weeks after complete recovery occurred.

Investigations during recent years present additional evidence of the possible pathogenicity of several types of microorganisms that are not as yet generally recognized as a cause of enteric diseases. For instance, *B. alkalescens*, formerly considered to be nonpathogenic, has now been shown to cause inflammatory lesions of the intestinal canal (Nabarro and Edward,[9] de Assis,[10] Felsen and Wolarsky[11]). Similarly, Coleman[12] described as a cause of enteritis a nonmotile, Gram-negative bacillus which ferments lactose slowly. That Gram-negative bacilli of doubtful

pathogenicity are not rarely found in the intestinal canal of infants and children with diarrhea may be seen from the bacteriologic studies carried out at the laboratories of the Children's Hospital. Of fifty-four specimens of feces from children with diarrhea which contained enteric bacilli other than *B. coli* and *B. aerogenes*, twenty-two showed recognized enteric pathogens, while thirty-two contained doubtful enteric pathogens. The results are summarized in Table III. These observations indicate the necessity of careful bacteriologic studies of *all* organisms in cases of enterocolitis. Only then will it be possible to determine the incidence of the "doubtful pathogenic" members of the enteric group of microorganisms and to further elucidate the relationship of these organisms to enteric diseases.

TABLE III

INCIDENCE OF ENTERIC BACILLI EXCEPT B. COLI IN 54 SPECIMENS OF FECES OF CHILDREN WITH DIARRHEA

A. Recognized Enteric Pathogens	
Typhoid bacillus	4
Paratyphoid bacillus	3
Flexner dysentery bacillus	8
Sonne bacillus	5
Newcastle bacillus	2
Total	22
B. Doubtful Enteric Pathogens	
Morgan bacillus, Type I	9
Morgan bacillus, Type X	5
Morgan bacillus, Type XII	2
Morgan bacillus, Type XIV	6
B. alkalescens	3
B. proteus	4
B. pyocyaneus	1
B. coli anaerogenes	2
Total	32

SUMMARY

1. Six cases of acute enterocolitis in infants are presented from whom Morgan bacillus, Type I, but none of the recognized enteric pathogens were isolated. A seventh patient has been included because of circumstantial evidence of infection with Morgan bacillus, Type I.

2. Four of the seven patients died. The post-mortem examinations revealed severe pseudomembranous enterocolitis in three cases and catarrhal enterocolitis in one case.

3. Two of the patients were twins who developed enterocolitis at the same time and whose mother harbored Morgan bacillus, Type I, in the intestinal canal.

4. One patient became a carrier of Morgan bacillus, Type I.

5. The incidence of Morgan bacilli and other doubtful enteric pathogens in the feces of children with diarrhea is presented.

6. The pathogenic significance of Morgan bacilli in enteric and other diseases is discussed.

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GONOCOCCAL CONJUNCTIVITIS IN CHILDREN

A Comparison of Treatment With Sulfanilamide and Sulfapyridine, With a Note on Sulfathiazole

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WITHIN the past four years there has been a radical change in the methods of treatment of gonococcal conjunctivitis. Prior to this the last outstanding advance in the management of this disease was made, more than half a century earlier, when the Créde method of prophylaxis against ophthalmia neonatorum was introduced. The prophylactic use of silver nitrate in the eyes of newborn infants brought about a great reduction in the incidence of the disease but did not eliminate it. There continued to be a distressing number of patients so afflicted; their treatment—dependent chiefly on cleansing irrigations and local antiseptics—was prolonged, and partial or complete loss of vision was all too frequent.

The introduction of the sulfonamide drugs into our therapeutic armamentarium has recently caused a vast change in the picture, the ultimate extent of which is not yet evident. Shortly after sulfanilamide was introduced in the United States, Dees, and Colston[1] showed that it was potent in the treatment of gonococcal infections. This report was followed rapidly by those of Hageman,[2] Newman,[3] Levy,[4] Willis,[5] and others who reported uniformly successful results in the treatment of gonococcal conjunctivitis with sulfanilamide. Barbour and Towsley[6] reported fifteen cases of gonorrheal conjunctivitis treated before the advent of sulfanilamide and fifteen subsequent cases treated with the drug and reviewed fifty-five additional cases so treated that were reported in the literature. In their series, the administration of sulfanilamide orally reduced the time from the beginning of treatment until negative smears were obtained from 25.5 to 4.8 days; it reduced the period of hospitalization from 30.7 to 8.3 days; and it reduced the incidence of corneal ulcers from 33.3 per cent to 6.6 per cent, and the incidence of significant loss of vision from 26.6 per cent to 0. Two, or 13.3 per cent, of their control patients were left blind. Their personal results with the use of sulfanilamide were almost identical with the combined experience of the authors whose papers they reviewed.

At the Gallinger Municipal Hospital sulfanilamide has been used in the treatment of gonorrheal conjunctivitis since 1938. The results with this method of treatment were, in general, quite satisfactory. However, there was an occasional patient in whom the disease was resistant to sul-

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fanilamide therapy, and it was our feeling that the ideal therapeutic agent had not yet been discovered. Shortly after sulfapyridine became available to us, early in 1939, three patients with gonorrheal conjunctivitis were found to be refractory to treatment with sulfanilamide but responded dramatically to sulfapyridine when it was administered (Cases 1, 2, and 3). This led us, when sulfapyridine became more abundantly available, to use it as the primary therapeutic agent in some of our patients with gonorrheal infections.

TABLE I

COMPARISON OF RACE AND SEX OF PATIENTS RECEIVING SULFANILAMIDE AND SULFAPYRADINE

TYPE TREATMENT	RACE AND SEX						
	TOTAL	WHITE			COLORED		
		TOTAL	MALE	FEMALE	TOTAL	MALE	FEMALE
Total	59	8	4	4	51	24	27
Sulfanilamide	26	3	0	3	23	10	13
Sulfapyridine	29	4	3	1	25	12	13
Sulfanilamide and sulfapyridine	4	1	1	0	3	2	1

TABLE II

COMPARISON OF THE AGE AND PLACE OF BIRTH OF PATIENTS RECEIVING SULFANILAMIDE AND SULFAPYRIDINE

TYPE OF TREATMENT	TOTAL	AGE AND PLACE OF BIRTH OF PATIENTS			
		NEWBORN			OLDER PATIENTS
		TOTAL	BORN IN HOSPITAL	NOT BORN IN HOSPITAL	
Total	59	46	36	10	13
Sulfanilamide	26	19	16	3	7
Sulfapyridine	29	24	19	5	5
Sulfanilamide and sulfapyridine	4	3	1	2	1

TABLE III

COMPARISON OF AGE AND SIZE OF PATIENTS RECEIVING SULFANILAMIDE AND SULFAPYRIDINE

TYPE OF TREATMENT	TOTAL	AGE AND SIZE OF PATIENTS			
		NEWBORN			OLDER PATIENTS
		TOTAL	TERM	PREMATURE*	
Total	59	46	34	12	13
Sulfanilamide	26	19	15	4	7
Sulfapyridine	29	24	17	7	5
Sulfanilamide and sulfapyridine	4	3	2	1	1

*Birth weight under 5 pounds 8 ounces.

The present paper presents our experience, from July 1, 1938, to Dec. 31, 1940, with fifty-nine patients with gonorrheal conjunctivitis treated with sulfanilamide, sulfapyridine, or both. A brief report of three patients treated with sulfathiazole early in 1941 is appended.

The two groups of patients, those receiving sulfanilamide and those receiving sulfapyridine, were not treated concurrently. That they were of relatively similar race, sex, age, and size, however, is shown in Tables I, II, and III. Of the total group, forty-six were newborn infants and thirteen were older children. It is of extraordinary interest that, of the newborn infants, twelve, or 26 per cent, were prematurely born. This incidence is several times higher than the incidence of premature births in the general population and may suggest that the Créde prophylaxis is often inadequately applied to very small infants. Thirty-six infants were born in this hospital. They constituted 0.75 per cent of the 4,715 infants born alive here during the period of the study.

DIAGNOSIS

The diagnosis of these patients was established by (1) the clinical finding of a reddened, edematous eye with a severe purulent conjunctival discharge and (2) demonstration of Gram-negative intracellular diplococci of typical morphology in the stained films of the eye discharge. Cultures of the eye discharge were made in a number of instances and, when positive for *Neisseria gonorrhoeae,* were considered positive evidence of the nature of the infection. However, not all eyes were cultured and not all cultures were positive. In the absence of a positive culture, typical clinical and microscopic findings were accepted as evidence of gonorrheal ophthalmia.

TREATMENT

All these patients were admitted to the Pediatric Ward of the Gallinger Municipal Hospital and were isolated in a special room reserved for such cases. Their general treatment was uniform throughout. The patients were kept in bed and were given general supportive care. The eyes were irrigated with warm boric acid solution or an 0.8 per cent solution of sulfanilamide frequently enough to keep the conjunctival sacs clear of discharge. A 10 per cent solution of argyrol was instilled into the conjunctival sac several times a day, usually half an hour before the eye was irrigated. In patients with unilateral involvement, the noninfected eye was protected from infection.

The chemotherapeutic agents were given immediately after smears had been taken and diagnosis had been established. Both sulfanilamide and sulfapyridine were given in equal dosage. This consisted of the immediate administration of an initial dose of from 0.3 to 0.6 grain per pound of body weight, followed by a daily maintenance dose of approximately 1.0 grain per pound of body weight. The maintenance dose was divided into six equal portions which were given at four-hour intervals.

If the clinical response was not favorable, the dosage of the drugs was increased to 3 or even 5 grains per pound of body weight per day. In a few cases the sodium salt of sulfapyridine was given intravenously to

promote a rapid increment of the drug in the blood stream. A 5 per cent solution was used, and doses of 0.4 to 0.5 grain per pound body weight were given every six to twelve hours as indicated.

Patients who did not recover within two weeks after the drugs were instituted were deemed to have failed to respond to the drug. In all cases, except in those which showed no response, the administration of the drug was continued until the clinical symptoms had subsided and smears were persistently negative. The patients were observed for two or more days after treatment was discontinued before they were discharged from the hospital.

RESULTS

There was a striking difference in the response of the patients to the two drugs. This was manifest in the number of patients in whom there was a favorable reaction, rather than the time relation of cure to therapy where this was effective. This is shown in Table IV. Of thirty patients treated with sulfanilamide, twenty-four (80 per cent) responded favorably and six (20 per cent) did not. Of twenty-nine patients who were treated primarily with sulfapyridine, twenty-eight (96.6 per cent) responded to the drug and one (3.4 per cent) was refractory. Four of the six patients who had been refractory to sulfanilamide were later given sulfapyridine. Three of these patients responded well, and one did not. Therefore, of a total of thirty-three patients who received sulfapyridine, thirty-one (94 per cent) reacted favorably and two (6 per cent) did not respond.

TABLE IV

A COMPARISON OF THE RESPONSE OF GONOCOCCAL CONJUNCTIVITIS TO TREATMENT WITH SULFANILAMIDE AND SULFAPYRIDINE

TYPE OF TREATMENT	TOTAL	RESPONSE TO TREATMENT										
		NO RESPONSE	RESPONSE									
			TOTAL	DAYS TO NEG. SMEAR								
				1	2	3	4	5	6	7	8	9	10+
Sulfanilamide	30	6	24	6	3	3	1	1	4	2	0	2	2
Sulfapyridine	29	1	28	12	4	3	2	3	2	1	0	0	1
Sulfapyridine after failure with sulfanilamide	4	1	3	2	0	0	0	0	0	0	1	0	0

There was no essential difference in the response of the patients who reacted favorably to the two drugs. Of the twenty-four patients who apparently were cured by sulfanilamide, twelve (50 per cent) gave negative smears within three days after therapy had been started. Likewise, of the thirty-one patients who responded to sulfapyridine, twenty-one (67.7 per cent) had negative smears within the same time. No patient who responded to either drug had positive smears for longer than eight days after treatment. Also, following the successful use of both drugs the eye symptoms were rapidly alleviated. Redness and swelling

usually showed a marked reduction within twenty-four hours, and the eye discharge was minimal if not absent within four days after the start of the treatment.

Complications were very infrequent in these patients. Corneal ulceration, which was so prominent and distressing under the older methods of treatment, was encountered only once in this series of patients (Case 3). This ulcer developed while the patient was receiving sulfanilamide. It responded promptly to sulfapyridine and foreign protein (milk injection) therapy. No other complications due to the gonococcus were encountered after treatment had been instituted. Nor were complications due to the chemotherapeutic agents much in evidence. Cyanosis was not infrequent, and vomiting occurred occasionally, but they caused little difficulty. One patient (Case 5) developed a morbilliform skin eruption, but withdrawal of the drug brought prompt relief.

Several infants, particularly among those born prematurely, acquired infections while in the hospital, and there were six deaths in the whole group. Each drug had been used in the treatment of three infants who met a fatal outcome. In four instances the eyes were clear, and treatment had been discontinued for several days before the onset of the fatal infection. In two instances, evidences of secondary infection developed while the therapeutic drugs were being administered, but the evidence at hand points to infection rather than sulfonamide toxemia as the cause of death. The morbidity and mortality among these infants were no greater than among normal infants of comparable age and size who were admitted to the hospital for maintenance during this same time.

DISCUSSION

The difference in response to sulfapyridine and sulfanilamide in these patients seems to be rather definite. Our results with sulfapyridine seem also to be comparable to those reported in the literature and, when combined with them, offer conclusive evidence of superiority of this drug. The first report of the use of sulfapyridine in gonorrheal conjunctivitis was that of Bowie,[7] who reported a rapid cure in a single case. One week later Michie and Webster[8] reported in greater detail on this patient and added one other who responded promptly to the drug. There are no reports of the use of sulfapyridine in gonorrheal ophthalmia in the United States.* From foreign literature, we have been able to collect reports of over forty-five cases so treated[7-22] (Table V). Good results were obtained in all but one of these. Including our own cases over seventy-eight patients have been treated with a prompt response by all but three. In no case did a corneal ulcer develop after sulfapyridine was started. Among 100 patients treated with sulfanilamide, including the patients in our series and those reported by Barbour and Towsley,[6] four developed corneal ulcers. It is our feeling

*Since this was written, Guyton and Woods[24] have mentioned two patients who responded to sulfapyridine after being resistant to sulfanilamide. They report that they now use sulfapyridine routinely in the treatment of gonorrheal conjunctivitis.

TABLE V

REVIEW OF GONOCOCCAL CONJUNCTIVITIS TREATED WITH SULFAPYRIDINE AS REPORTED PREVIOUSLY

AUTHOR	REF. NO.	NO. OF CASES TREATED	NO. OF CASES THAT RESPONDED PROMPTLY	NO. OF CASES THAT DID NOT RESPOND PROMPTLY	NO. CASES THAT DEVELOPED CORNEAL ULCER AFTER TREATMENT
Bowie	7	1	1	0	0
Michie and Webster	8	2*	2	0	0
Pautrier and Langier	9	1	1	0	0
Redslob, Marx, Diffenbach and Milaras	10	1	1	0	0
Chaniol and Barut	11	2	2	0	0
Sysi	12	11	10	1	0
Valdeaveleano	13	6	6†	0	0
Suarez-Gabard	14	5	5	0	0
Szinegh	15	3	3	0	0
Cecchetto	16	1‡	1	0	0
McLachlan and Thomson	17	2	2	0	0
Jensen	18	3	3	0	0
Thrane	19	1	1	0	0
Sloboziano and Herscovici	20	6	6	0	0
Puglisi-Duranti	21	1	1	0	0
Cislaghi	22	Not recorded§	All	0	0
Total		45+¶	44+	1	0

*Includes case reported by Bowie.[7]

†Two patients suffered relapses, but they responded promptly with further treatment.

‡Five additional patients responded promptly to local compresses of a suspension of sulfapyridine in warm water.

§There were fifteen patients with pneumococcal and gonococcal conjunctivitis.

¶Panneton[23] reported good results with insufflation of powdered sulfapyridine into the infected eye in gonococcal conjunctivitis.

that the results obtained with the use of sulfapyridine are definitely better than those obtained with any previous method of treatment.

TREATMENT WITH SULFATHIAZOLE

Since Jan. 1, 1941, three patients with gonorrheal conjunctivitis have been treated with sulfathiazole. They were a white male, aged 10 years, previously blind from an interstitial keratitis due to syphilis, a colored male infant born at term, and a colored female infant born after eight months gestation with a birth weight of 4 pounds 12 ounces. The latter two patients were aged 3 and 2 days, respectively, on admission. The diagnosis was established by the same means as in the above recorded series. The dosage of sulfathiazole was the same as that of sulfanilamide and sulfapyridine. In each instance there was remarkable improvement of the eye condition within twenty-four hours after therapy was begun. Smears free from gonococci were obtained from the eye discharges after one, six, and three days, respectively, in the three patients. There were no toxic manifestations from the drugs, and there were no bacterial complications in any of the three patients.

CASE REPORTS

The following detailed case reports present the records of patients refractory to one or the other of the drugs and are illustrative of the problems met in such instances:

CASE 1.—Infant to M. W. (A91677), a white male, weighing 5 pounds 12 ounces, was born in the hospital on Feb. 20, 1939. The patient's mother was known to have gonorrhea. Two drops of a 1 per cent solution of silver nitrate were instilled into each conjunctival sac immediately after birth, and this treatment was repeated after twenty-four hours. A few hours later the infant was found to have a purulent conjunctivitis of the right eye, with redness and edema. The eye was kept clean with boric acid irrigations and argyrol, but it did not improve. Stained films of the eye discharge showed many Gram-negative intracellular diplococci. On Feb. 23, 1939, when the infant was 3 days old, he was given sulfanilamide, the dose per pound of body weight being 0.5 grain initially, followed by 1 grain per pound per day divided into six equal doses. On March 8 the daily dose of sulfanilamide was increased to 2 grains per pound. Blood sulfanilamide levels were not determined. The infant's general condition was satisfactory, but the eyes continued to discharge pus freely, and the stained films continued to show Gram-negative intracellular diplococci. On March 10, sixteen days after treatment was instituted, sulfanilamide was discontinued, but irrigations and antiseptics were continued.

On March 15, five days later, sulfapyridine was started. The initial dose was 3 grains per pound, followed by a maintenance dose of 1.4 grains per pound per day. Eye smears, which had been positive on March 15, were negative on March 16 and thereafter. The discharge decreased rapidly and disappeared on the fourth day after sulfapyridine was given. The administration of the drug was continued until March 22, three days after the discharge had disappeared and six days after negative smears had been obtained. Three days later the infant was discharged in good health. There were no untoward reactions to the drug.

CASE 2.—H. P. (A92522), a colored male, aged 9 days was admitted to the Pediatric Service on March 8, 1939. The patient had been born in another institution, and the mother's condition was unknown. When the infant was 7 days old, he developed an acute purulent conjunctivitis. Two days later Gram-negative intracellular diplococci were found in stained films of the eye discharge. Three grains of neoprotosil had been given every four hours for thirty-six hours before transfer. On admission the patient was a well-developed, apparently premature infant that weighed 5 pounds 3 ounces. Both eyes were slightly swollen, with a moderate purulent discharge. Stained films of the eye discharge showed no organisms. The child was given supportive care and cleansing irrigations to the conjunctival sacs. On March 13, five days after entry, the discharge became more profuse and the eye smears showed Gram-negative intracellular diplococci. The infant was given sulfanilamide in the usual dosage; the frequency of eye irrigations was increased; and 10 per cent argyrol was used locally. The eye condition improved slightly, but the smears remained positive. On March 24, after eleven days of sulfanilamide treatment, the sulfanilamide was discontinued, and sulfapyridine was instituted in the same dosage, 0.7 grain per pound immediately followed by 1.3 grains per pound per day. The following day the eye smear was negative, and the discharge had ceased. The sulfapyridine was continued for five days, and the infant was discharged in good health six days after sulfapyridine therapy was started. There were no untoward effects. There were no determinations of the blood concentration of either sulfanilamide or sulfapyridine.

CASE 3.—V. L. (A93181), a colored female, aged 3 years, was admitted to the Pediatric Service on March 22, 1939. She had been well until two days before entry

when she awoke with a discharge from the left eye. The eye gradually became red and swollen; it was filled with a creamy yellow pus. On admission the patient had a temperature of 102° F. She was acutely ill. The left eye was red, swollen, and tender with a profuse purulent discharge. The right conjunctiva was injected but showed no exudate. Stained films of the eye discharge showed Gram-negative intracellular diplococci. Eye culture yielded no *Neisseria gonorrhoeae.*

The patient was started immediately on frequent warm boric acid eye irrigations, preceded by the instillation of 10 per cent argyrol into the conjunctival sac. The temperature fell rapidly to normal, and there was slight improvement of the eye condition, but the smears continued to be positive. On March 27 the daily dosage of sulfanilamide was increased to 2.4 grains per pound body weight. On March 30 a small ulcer appeared on the lower nasal quadrant of the left cornea. The following day the condition had become somewhat worse. Sulfanilamide was discontinued and replaced by sulfapyridine, 0.6 grain per pound body weight per day. Atropine was used to dilate the pupil; the conjunctiva was kept filled with boric acid ointment; and irrigations were reduced in frequency. Sterile milk was injected intramuscularly. The corneal ulcer enlarged for one day and then became stationary in size. The conjunctival discharge lessened rapidly and was imperceptible on the sixth day after sulfapyridine; the corneal ulcer began to show definite improvement on the same day. Eight days after sulfapyridine therapy the eye smears—the first taken since the appearance of the ulcer—were negative. The patient continued to progress favorably. Three weeks after sulfapyridine was instituted, she was discharged with only small corneal scars that caused no significant loss of vision. There were no untoward reactions to the drug. No determinations of the concentration of either sulfanilamide or sulfapyridine in the blood were made.

CASE 4.—Infant to E. B. (B11205), a colored male, was admitted to the Pediatric Service on March 22, 1940, at the age of 6 days. The mother had received treatment for syphilis during her pregnancy; she denied having gonorrhea. The infant was born in another institution from which he was discharged on the fifth day of life, one day after developing a purulent conjunctivitis. On admission the patient had a purulent conjunctivitis of the right eye. The left eye was clear. Stained films of the eye discharge contained Gram-negative intracellular diplococci; cultures yielded *Neisseria gonorrhoeae.* The patient was given the usual dosage of sulfanilamide on admission. Five days later the concentration of free sulfanilamide in the blood was 6.9 mg. per cent. There was no improvement in the patient's condition, and on March 30, eight days after the administration of sulfanilamide, it was felt that the progress with this drug was unsatisfactory. Consequently, the sulfanilamide was omitted, and the patient was given sulfapyridine, 1.5 grains per pound per day. The patient received no large initial dose, however, and the sulfapyridine concentration in his blood was 2.2 mg. per cent on April 1, and 2.0 mg. per cent on April 3. On April 9 the blood level had risen to 4.3 mg. per cent. The eyes showed no improvement, and smears and cultures remained positive. On April 17 the sulfapyridine dosage was increased to 4 grains per pound per day, and the blood level rose to 16.0 mg. per cent. There still was no remarkable improvement, however. The local therapy was continued, and the eyes gradually improved. Smears became negative thirty-eight days after entry, and the patient was discharged in good condition after forty-nine days in the hospital.

The blood level of sulfanilamide in Case 4 was thought to have been sufficient to cause a favorable response, but this did not occur. It is possible that the failure to give a larger initial dose of sulfapyridine, which resulted in low levels early in the course of treatment with that drug, allowed the organism to become tolerant of sulfapyridine to the extent

that the later high levels were ineffective. The organism may have been resistant to this drug initially, as it was to sulfanilamide.

CASE 5.—V. B. (B21608), a white female, aged 8 years, was admitted to Pediatric Service on Oct. 19, 1940. She had been well until two days before entry, when she developed a purulent conjunctivitis, which became more severe. A cousin, who slept with the child, had gonococcal vaginitis. On admission there was a severe right conjunctivitis. Stained films of the discharge contained many Gram-negative intracellular diplococci; cultures were positive for *Neisseria gonorrhoeae*. The patient was given frequent eye irrigations and local antiseptics and was given sulfapyridine 0.6 grain per pound of body weight immediately and 1.0 grain per pound per day. There was slight improvement of the eye, but this was not satisfactory. The blood sulfapyridine level on October 21, two days after treatment, was 1.6 mg. per cent, and the next day was 2.0 mg. per cent. On October 21 the patient was given the sodium salt of sulfapyridine intravenously, 0.4 grain per pound of body weight every twelve hours. The concentration of sulfapyridine in the blood still remained low, and the intravenous sodium sulfapyridine was increased to a total of 1.66 grains per pound per day; nevertheless, the highest concentration recorded was 3.6 mg. per cent. There was only slight improvement of the eye when, on October 27, the patient developed a morbiliform skin eruption as a manifestation of sulfapyridine toxemia. The administration of the drug was discontinued and the rash disappeared, only to reappear when the drug was administered again. Thereafter no sulfonamide drugs were used. Local applications were continued; the smears became negative after thirty-five days; and the patient was finally discharged in good condition thirty-eight days after entry.

The failure of the treatment of the patient in Case 5 was evidently due to her very rapid excretion of the drug. Even with rather heroic procedures we were unable to maintain an effective concentration of the drug in her blood.

SUMMARY

The results of treatment of sixty-two patients with gonorrheal conjunctivitis are reviewed. Of thirty patients who received sulfanilamide, 24 showed rapid recovery. Thirty-three patients, including four who failed to respond to sulfanilamide, received sulfapyridine. A rapid recovery was experienced by thirty-one. Three patients were treated with sulfathiazole; all responded promptly. Only one corneal ulcer developed, this being in a patient on sulfanilamide therapy. Reports on over forty-five cases of gonorrheal conjunctivitis treated with sulfapyridine have been collected from the literature. The results in these cases were comparable to those in the current series.

CONCLUSION

It is suggested that sulfapyridine is superior to sulfanilamide or any previously used agent in the treatment of gonorrheal conjunctivitis. Sulfathiazole as a therapeutic agent merits further trial.

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THE TREATMENT OF GONOCOCCAL VULVOVAGINITIS IN CHILDREN

A Report of 18 Cases Treated by the Implantation of Estradiol Benzoate

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ALTHOUGH numerous therapeutic agents have been tried in the treatment of prepubertal gonococcal vulvovaginitis, the most nearly satisfactory one to date is estrogenic hormone. The work of Allen,[1] who demonstrated that thickening of the epithelial layer could be produced in the vagina of immature animals by estrogen, was followed by that of Lewis,[2] who was the first to apply this knowledge to the treatment of gonococcal vulvovaginitis in children. Since that first practical application Te Linde[3] has established this type of therapy as the one of choice. Although Te Linde experimented with estrogen by mouth, by hypodermic use, and in suppository form, he felt that the last was the method of choice. Recently Russ and Collins[4] reported a small group of cases treated with stilbestrol orally with encouraging results. This latter treatment may prove the one of choice if further studies confirm its merit. However, the use of either hypodermic therapy or vaginal suppositories has obvious disadvantages.

In 1939 Salmon and his co-workers[5] published a brief report on the use of estradiol benzoate implanted subcutaneously in a group of women with menopausal symptoms. Complete relief of symptoms usually began within two weeks and at the time of their report had persisted from sixty to ninety-eight days after the implant. Objective evidence of the biologic effect of the estrogenic substance so used was noted in vaginal smears as early as four days after the implant. Atrophy cells and leucocytes began to diminish in number and were replaced by large squamous epithelial cells exhibiting characteristics of smears of normally menstruating women. The authors attributed their excellent results to the slow rate of absorption and excretion of the hormone.

It occurred to us that such a method of employment of estrogenic material should prove effective in the treatment of prepubertal gonococcal vulvovaginitis. Consequently such a study was begun, and this paper is a report of eighteen cases so treated.

MATERIAL AND PLAN OF STUDY

There were eighteen colored females ranging in age between 4 months and 10 years. All were treated in the Pediatric Wards of the Philadelphia General Hospital and were admitted several days prior to

From the Pediatric Department of the Philadelphia General Hospital.

therapy, during which time only perineal flushings with boric acid were used. None of the patients was among those treated in our previous studies.[6, 7] All patients had a vaginal discharge that showed Gram-negative intracellular diplococci. No cases with evidence of arthritis or disease of the pelvic organs were included in the study. The first patient was treated Jan. 11, 1940, and the last on Nov. 25, 1940.

Smears for the study of bacteriology and vaginal epithelium were taken twice weekly. The hospital laboratory examined the smears for gonococci, while one of us, who purposely remained unaware of the time that treatment was instituted, studied the smears for the changes in epithelium. We felt this latter precaution was very important in evaluating the results. The patients remained in the ward about four weeks and later were followed in the Vaginitis Clinic.

TABLE I

PATIENT	AGE	DATE OF IMPLANT (1940)	NO. OF DAYS AFTER IMPLANT BEFORE APPEARANCE OF SQUAMOUS EPITHELIUM	NO. OF DAYS AFTER IMPLANT BEFORE APPEARANCE OF SQUAMOUS EPITHELIUM AND NEGATIVE SMEAR	SECONDARY SEX CHANGES
T. McK.	9 yr.	Jan. 11	11	11	Moderate pubic hair and breast enlargement
M. R.	4 mo.	Feb. 13	5	6	Slight bloody vaginal discharge—twice
F. J.	5 yr.	March 25	7	14	None
B. F.	2 yr.	April 16	6	6	None
E. U.	8 yr.	May 11	16	44	None
A. C.	7 yr.	May 13	10	21	Moderate breast enlargement
A. B.	3 yr.	June 28	10	17	None
L. T.	8 yr.	July 12	3	10	None
B. S.	3 yr.	July 22	7	7	Moderate breast enlargement
A. M.	2½ yr.	Aug. 1	6	11	Moderate breast enlargement
L. B.	7 yr.	Aug. 29	7	18	None
J. T.	2½ yr.	Sept. 12	18	32	Moderate breast enlargement
A. H.	10 yr.	Sept. 20	10	10	None
M. H.	10 yr.	Sept. 20	5	5	None
D. C.	6 yr.	Oct. 8	13	14	None
D. W.	4 yr.	Oct. 22	6	7	None
A. B.	7 yr.	Nov. 25	7	8	None
J. B.	8 yr.	Nov. 25	7	8	None

TECHNIQUE OF IMPLANTATION

The upper right quadrant of the buttock was chosen as the best site for the implant because of the large amount of fat. The estrogen used was estradiol benzoate,* which is fat soluble, in pellet form. Each pellet represented 90,000 International units. Sterilization was effected by autoclaving at 15 pounds of pressure for fifteen minutes at 250° F.

*Supplied by The Schering Corporation, Bloomfield, N. J.

After proper preparation of the skin an incision about ¾ inch long was made through the skin, and hemostasis was effected. Then a pocket about ½ inch deep was made in the fat, and the pellet deposited. The wound was carefully closed with a silk suture which was removed on the fifth day. No wound complications occurred.

Fig. 1.

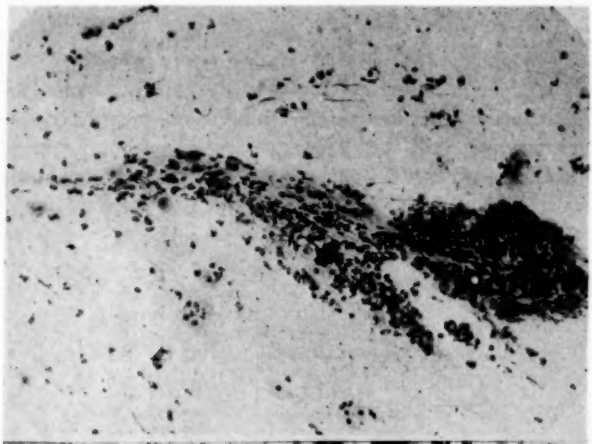
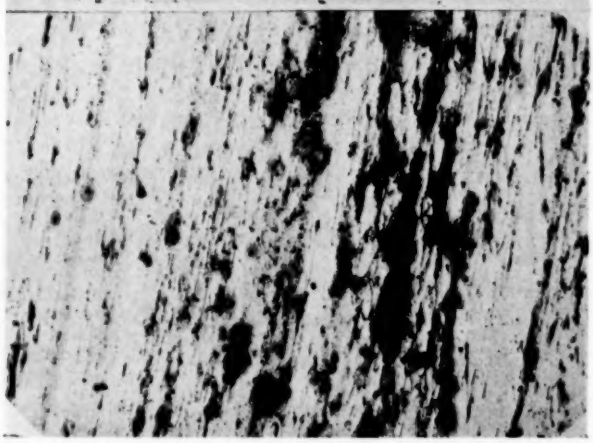


Fig. 2.



Figs. 1-6.—Photomicrographs illustrating effects of implants of estradiol benzoate upon prepubertal vaginal epithelium.

Fig. 1.—Smear before implantation showing preponderance of leucocytes, mucus, and few epithelial cells.

Fig. 2.—Photomicrograph taken four days after implantation showing no material change.

RESULTS

The results obtained from this treatment were very encouraging (Figs. 1 through 6). Within an average of 8.3 days after the implant squamous epithelium began to appear. Within an average of 13.6 days the cases

showed squamous epithelium with negative smears for the gonococcus. The greatest number of days required for the squamous epithelium cells to appear was eighteen, while the combination of the cellular changes plus a negative smear for the gonococcus required forty-four days in one case. The vaginal discharge began to change to one mucoid in character

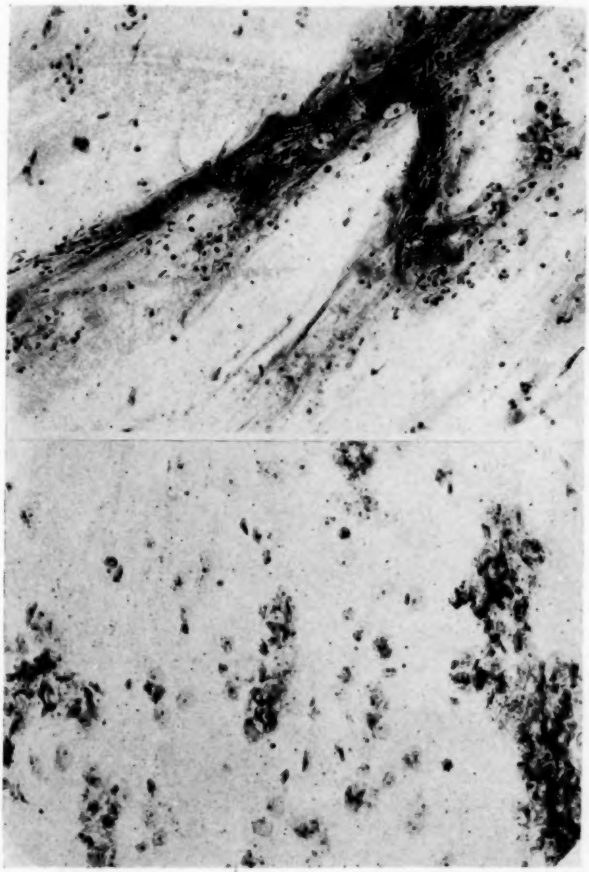


Fig. 3.

Fig. 4.

Fig. 3.—Photomicrograph taken eight days after implantation showing fewer leucocytes, more mucus, and round epithelial cells.

Fig. 4.—Photomicrograph taken eleven days after implantation showing many squamous epithelial cells, few leucocytes, and shreds of mucus.

as the hormone effect took place. Not a single case showed a positive smear for the gonococcus once the smear was negative. None of the cases showed any demonstrable ill effects from the treatment, and no wound complications occurred. The effect on breast development will be discussed later.

DISCUSSION

Estrogenic hormone therapy results in a higher percentage of cures, with fewer recurrences than other methods of treatment. The final decision as to how best to employ such therapy cannot be made until further studies are reported. The method we have employed seems to be a sound one, but the number of cases treated is small.

Fig. 5.

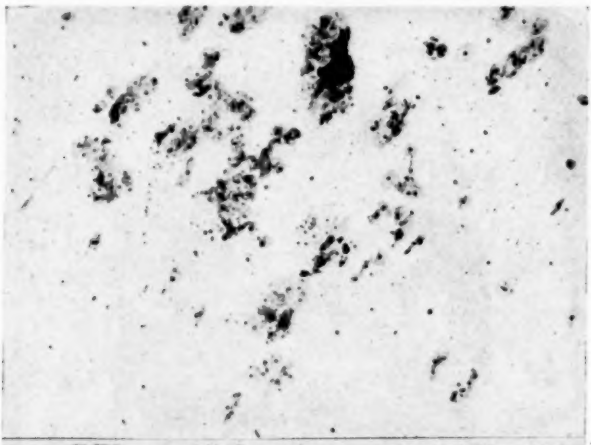


Fig. 6.

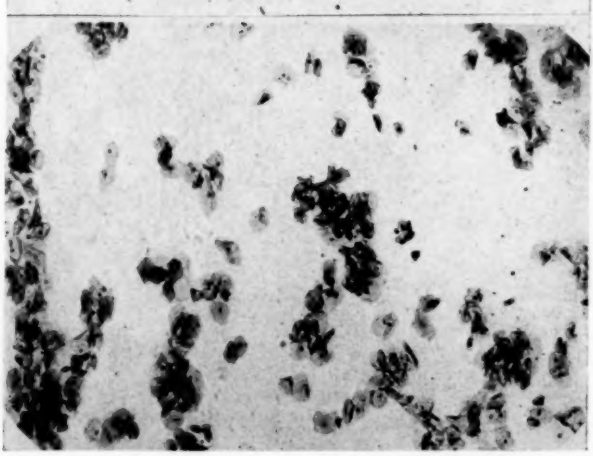


Fig. 5.—Photomicrograph taken fifteen days after implantation showing many squamous epithelial cells, some in "flakes."

Fig. 6.—Photomicrograph taken eighteen days after implantation showing cellular elements essentially the same as on fifteenth day.

The number of units of estrogen used was arbitrary since this is the first time this type of therapy has been used in children with gonococcal vulvovaginitis. At the beginning we implanted two children with 45,000 International units. Neither showed any change in the type of vaginal epithelium. Consequently, the dose was doubled in the succeeding cases.

The possibility of harmful effect from any glandular preparation must always be kept in mind. Four of our patients showed moderate breast enlargement, and one of the four developed a few pubic hairs. The breast development has gradually regressed. Another patient, the 4-month-old infant, had a very slight bloody discharge on two occasions. Te Linde[3] felt that none of his cases showed any permanent harmful effect.

Another aspect of the method herein employed is the duration of the vaginal epithelium changes. We hope to make a report on this at a later date. From biopsies of vaginal tissue in his cases Te Linde[3] found a return to normal epithelium in from four to six weeks after treatment was stopped. Some of our cases have been implanted too recently to allow an adequate follow-up. However, of the ones treated at the beginning of the study, none has shown any recurrence or reinfection. This seems most encouraging.

SUMMARY

Eighteen cases of gonococcal vulvovaginitis in children were treated with estradiol benzoate by implanting a pellet representing 90,000 International units in the fat of the buttock.

Within an average of 8.3 days after the implantation squamous epithelial cells began to appear. Within an average of 13.6 days after the implantation all cases showed squamous epithelial cells and negative smears for the gonococcus.

No recurrences of the infection have occurred to date.

One patient had slight vaginal bleeding on two occasions. Four others showed moderate breast enlargement, and one of these developed a few pubic hairs.

CONCLUSIONS

We believe that the method herein described should prove an easy, effective, inexpensive, and reasonably safe method of treating prepubertal gonococcal vulvovaginitis.

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THE VALUE OF SULFANILAMIDE AND SCARLET FEVER ANTITOXIN IN THE TREATMENT OF SCARLET FEVER

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INTRODUCTION

THE value of sulfanilamide in scarlet fever has been the subject of many investigations during the past few years. The reports have been controversial, leaving the final answer in doubt. The early investigators proceeded cautiously in the administration of this comparatively unknown drug and used different criteria of dosage and toxicity than prevail at present. We had a similar experience. A series started in 1938 by us at our hospital was not presented due to the large number of cases in which the drug had been discontinued within twenty-four to forty-eight hours because of cyanosis. In the light of the present knowledge of sulfanilamide and with the continued uncertainty as to its efficacy in scarlet fever, further investigation was deemed necessary.

MATERIAL AND SCOPE

This study was made on 680 patients admitted to Kingston Avenue Hospital from February through May, 1940. These patients were drawn predominantly from the lower economic strata and, according to the local health regulations, were isolated for a period of at least twenty-one days from the onset of the disease. At this season scarlet fever is normally at its height in New York, and during this year there was an unusually large number of cases, mostly of a comparatively mild nature.

The general clinical picture and impression of the observer were used as a basis for the classification rather than any rigid standards. The use of definite temperature levels seemed unwise because of the many variable factors apart from the severity of the disease, such as time of day, therapy previous to admission, the long ambulance ride before admission, etc.

The cases were divided into "mild," "moderate," and "severe" groups. The following criteria of classification were used by the admitting physicians: (A) "mild": low or no fever, slight or absent toxicity, no complications. (B) "moderate": fever, toxicity, complications present on admission. (C) "severe": marked prostration and toxicity or life-threatening complications.

During the entire period of survey only three cases fell into this last group. Since the number was so small, no conclusions were drawn

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as to the efficacy of different therapeutic measures in this severe group, and they are not included in this series.

The ages of the patients ranged from 10 months to 41 years; the average being 8.21 years. Of these, 28.1 per cent were under 5 years. There were 370 males and 310 females.

PLAN OF PROCEDURE

Patients classified as "mild" were divided into two groups according to therapy: (a) control (symptomatic treatment) and (b) sulfanilamide. Because of the strain on laboratory facilities, twice as many patients were placed in the control group. Patients classified as "moderate" were divided into four groups according to therapy: (a) control, (b) sulfanilamide, (c) scarlet fever antitoxin, and (d) sulfanilamide plus scarlet fever antitoxin.

METHOD OF ADMINISTRATION

The dosage of sulfanilamide was computed as follows: 1 grain per pound of body weight per day (maximum 120 grains) administered in six equal parts. The initial dose was one-half the estimated daily dose. Equal quantities of sodium bicarbonate were given with the sulfanilamide. The drug was administered in these amounts until the temperature remained below 100° F. for forty-eight hours, after which the dosage was halved and continued until the patient had received sulfanilamide for a total of two weeks.

All patients receiving sulfanilamide had a complete blood count on admission. A white blood count, hemoglobin determination, and urine examination were done every other day thereafter. Sulfanilamide blood concentration was done on the third hospital day.

The average total dose of sulfanilamide per patient was 429.9 grains (28.66 Gm.). The average sulfanilamide blood concentration was 4.89 mg. per cent.

Cutaneous and ophthalmic tests for horse serum sensitivity were done on patients who were to receive antitoxin. We found occasional positive skin tests, but no positive eye tests. We placed our reliance on the latter test. Scarlet fever antitoxin (Lederle) in dosage of 9,000 units was given intramuscularly with an adequate amount of adrenalin chloride 1:1,000 with no immediate untoward results.

RESULTS

In evaluating the results of any scarlet fever investigation, the question of what constitutes a complication is of extreme importance. In this series we encountered the following complications and included them if they satisfied the accompanying criteria:

1. Otitis media—(a) inflamed eardrum with distortion or obliteration of landmarks accompanied by fever for which no other cause could be found; (b) discharging ear.

2. Adenitis—enlarged, tender glands developing after admission and accompanied by fever.

3. Sinusitis—swelling or tenderness over sinuses and/or x-ray evidence of sinus pathology, accompanied by fever.

4. Rhinitis—profuse purulent nasal discharge.

5. Mastoiditis—proved by operation.

6. Secondary pharyngitis or tonsillitis—clinical evidence of acute pharyngeal or tonsillar inflammation, newly developed after admission and accompanied by fever.

7. Arthritis—joint pain and swelling developing in patients who did not receive antitoxin.

8. Pneumonia—clinical and x-ray evidence.

9. Myocarditis—patients developing tachycardia or bradycardia out of proportion to temperature, associated with new murmurs, electrocardiographic findings or x-ray evidence of cardiac enlargement, with regression before discharge.

10. Empyema—proved by aspiration.

11. Recurrent scarlet fever—reappearance of scarlet fever.

12. Nephritis—consistent appearance of albumin, red blood cells, and casts in the urine, with no previous history of kidney disturbance.

13. Superficial skin infections—paronychiae, impetigo, superficial abscesses.

14. Unexplained fever—It has been our experience that often in the third week of the disease, patients almost ready for release from isolation exhibit fever between 100° and 101° F., for which no adequate cause can be found. While this is of no lasting significance, nevertheless it prolongs the hospital stay unduly and is a definite factor in the management of the disease.

Mild Group.—In Table I are listed the results of our investigation in the mild group of cases. The age groups in the control and treated cases were approximately equal. The total febrile period was equal in the two groups; this is in conformity with the observations of the great majority of previous observers. The difference in isolation period, 24.25 days in the control group, as compared with 22.87 days in those treated, is significant when we consider that the minimal isolation period is twenty-one days. When twenty-one is subtracted from the other figures, it is shown that the isolation period was prolonged 3.25 days in the control group as compared with 1.87 days in the treated cases.

A glance at the figures for total complications reveals a striking difference. The percentage of complications in the control cases was 33.3 per cent as against 13.1 per cent in the treated group. The incidence of the most frequent complication, otitis media, was substantially reduced in the treated cases: 9.3 per cent in controls and 2.07 per cent in treated cases. Adenitis occurred in 8.16 per cent of the controls and in 4.14 per cent of the treated cases. The other complications did not occur in sufficient numbers to warrant any conclusions, but the differ-

TABLE I

MILD GROUP

	CONTROL	SULFANILAMIDE
No. of cases	294	145
Average age in years	8.25	7.35
Per cent under 5 years	26.8	30.3
Mean day of disease on admission	3.18	3.00
Febrile period in hospital (in days)	1.83	2.08
Total febrile period (in days)	5.01	5.08
Duration of isolation (in days)	24.25	22.87
No. of complications	98	19
Percentage of complications to total No. of cases	33.3	13.1
No. of patients with complications	85	18
Percentage of patients with complications	28.9	12.4
Otitis media	28	3
Adenitis	24	6
Sinusitis	8	1
Secondary pharyngitis and tonsillitis	2	1
Rhinitis	7	3
Mastoiditis	2	0
Arthritis	1	2
Myocarditis	2	0
Pneumonia	4	0
Recurrent scarlet fever	0	1
Nephritis	1	0
Superficial skin infections	11	1
Unexplained fever	8	1

ences between the incidence of superficial skin infections (3.7 per cent in control cases, 0.7 per cent in treated cases) and unexplained fever (2.7 per cent in control group, 0.7 per cent in treated group) seem worthy of note.

Moderate Group.—The results obtained in this group are shown in Table II and closely parallel those obtained in the "mild" cases.

The average ages in each group were approximately the same, except for the slightly more advanced age in the scarlet fever antitoxin group. The total febrile periods were approximately equal in all groups, but slightly longer in the control group (7.43 days), and least in the scarlet fever antitoxin group (6.29 days). The isolation periods were approximately the same in the treated groups (25.5 days) but were appreciably greater in the control group (29.7 days).

The total incidence of complications was definitely diminished in all treated groups, the greatest effect being noted in those receiving sulfanilamide. The percentages of complications in the two groups (sulfanilamide 24.1 per cent, and scarlet fever antitoxin plus sulfanilamide 23.8 per cent) were practically equal but were approximately one-half that found in the scarlet fever antitoxin group (41.5) and one-third that found in the control group (60.3).

There were such small numbers of individual complications that definite conclusions are unwarranted. However, we may state that the incidence of otitic complications in the sulfanilamide-treated groups (7.4 per cent and 6.5 per cent) was approximately half that found in the other two groups (12.3 per cent and 13.8 per cent). The incidence

of adenitis is apparently at variance with our other results. The incidence in the control group was 10.96 per cent, scarlet fever antitoxin 9.25 per cent, sulfanilamide 5.55 per cent, sulfanilamide plus scarlet fever antitoxin 13 per cent. A possible explanation of these figures may be that some of the cases in the last mentioned group were manifestations of serum disease, although we found no other evidence to support this view.

A comparison of the figures for febrile period, duration of isolation, and incidence of complications in the "mild" and "moderate" groups affords confirmation of the validity of the classification regarding severity.

TABLE II

MODERATE GROUP

	CONTROL	SCARLET FEVER ANTITOXIN	SULFANILAMIDE	SCARLET FEVER ANTITOXIN AND SULFANILAMIDE
No. of cases	73	65	54	46
Average age in years	7.8	10.97	7.5	8.28
Percentage of patients under 5 years	31.5	23.1	37	19.8
Mean day of disease on admission	2.96	2.71	3.54	3.13
Febrile period in hospital (in days)	4.47	3.58	3.67	3.82
Total febrile period (in days)	7.43	6.29	7.21	6.95
Duration of isolation (in days)	29.7	25.5	25.35	25.79
No. of complications	44	27	13	11
Percentage of complications	60.3	41.5	24.1	23.8
No. of patients with complications	32	20	13	10
Percentage of patients with complications	43.9	30.8	24.1	21.8
Otitis media	9	9	4	3
Adenitis	10	6	3	6
Sinusitis	8	5	0	1
Secondary pharyngitis and tonsillitis	0	2	2	0
Rhinitis	1	1	0	0
Recurrent mastoiditis	1	0	0	0
Arthritis	2	0	1	0
Myocarditis	1	0	1	0
Pneumonia	1	1	1	0
Recurrent scarlet fever	1	0	0	0
Empyema	1	0	0	0
Superficial skin infections	6	1	1	1
Unexplained fever	3	2	0	0

LITERATURE

A review of the reports in the literature reveals varied results. Our observations agree with those reports which attest to the efficacy of sulfanilamide in scarlet fever. Other investigators found it of little or no value.

Several observers report that sulfanilamide and its derivatives have no beneficial effect on the acute febrile period or on complications. Some administered the drug only during the acute stage[2, 3, 10] while others gave it for an extended period varying from two to four weeks.[1, 4, 7, 8]

TABLE III

PERCENTAGE OF COMPLICATIONS AS REPORTED BY VARIOUS AUTHORS

SOURCE	CONTROL	SCARLET FEVER ANTITOXIN	SULFANILAMIDE	SCARLET FEVER ANTITOXIN AND SULFANILAMIDE
Wesselhoft and Smith	72		66	
Schwentker and Waghelstein	17	15	26	
Peters and Havard	56		35‡	
Sako, Dwan, and Platou	41		8	
Rascoff and Nussbaum	30.9	17.3	14.6	15.7
Hogarth	33	23.2		28‡
Hamilton and Togasaki		15.6*	11.1	
French	60.7		61.0	
Benn	31		18.9	
Thenebe	24.5†	22.2†	9.7	
Gordon, Solomon, and Pearlman (mild)	33.3		13.1	
Gordon, Solomon, and Pearlman (moderate)	60.3	41.5	24.1	23.8

*Convalescent serum.
†Control in different years.
‡Used proseptasine (benzyl-sulfanilamide).

Other reports[5-11] indicate that sulfanilamide or its derivatives have some advantage in the treatment of scarlet fever in that there is a reduction in the number and severity of complications.

Sako, Dwan, and Platou[7] found a definite reduction in complications (sulfanilamide, 8 per cent; control, 41 per cent). These figures have been criticized because of the high incidence of nephritis (11 per cent) in the control group, but even after the nephritic cases are subtracted the results are still significant.

Rascoff and Nussbaum,[12] in a controlled series at this hospital, found a slight reduction in the incidence of complications in the sulfanilamide-treated patients. They felt that the number of cases was too small and the decrease in complications not impressive enough for definite conclusions.

TOXIC REACTIONS

Table IV gives a detailed analysis of the toxic manifestations of sulfanilamide encountered which necessitated cessation of chemotherapy.

TABLE IV

	NO. OF CASES	PERCENTAGE OF CASES
Total No. of patients receiving sulfanilamide	245	
Total complications	49	20
Rash	35	14.3
Cerebral symptoms	4	1.6
Pyrexia	3	1.2
Drop in hemoglobin	7	2.8

In this series a total of 245 patients received sulfanilamide. Of this number, forty-nine (20 per cent) developed complications related to

the drug. This is in agreement with the findings of French,[4] who in a similar series noted toxic manifestations in 21.1 per cent of the cases.

A generalized morbilliform rash was the most frequent toxic reaction to the drug. This occurred in thirty-five cases, representing 14.3 per cent of all patients receiving sulfanilamide and 71 per cent of those with toxic reactions. Other types of rashes have been observed following sulfanilamide administration: varicelliform,[13, 14] bullous,[15, 16] scarlatinal,[18] purpuric,[18] and exfoliative,[17] but those encountered in our series were always morbilliform. In association with this rash we noted pyrexia in 40 per cent and conjunctivitis in many instances.

The time of appearance of the rash is of interest in that it appeared from the seventh to the fourteenth day and in 57 per cent of cases on the tenth day of administration. This conforms closely to the figures of others,[4, 19] and is illustrated in Fig. 1.

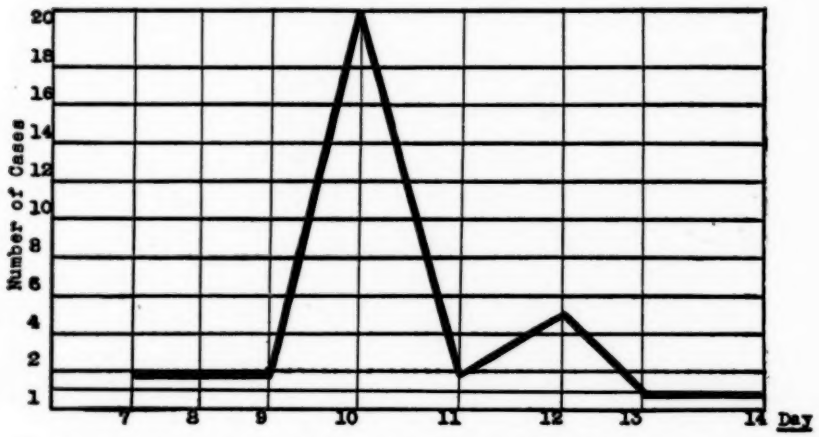

Fig. 1.—Chart showing onset of rash following the administration of sulfanilamide. The number designates the day upon which the rash appeared.

In the beginning of the series we discontinued the drug in four cases (1.6 per cent) because of cerebral manifestations (delirium or marked apathy). Patients with similar symptoms were encountered as the series progressed, but the drug was continued with no further untoward effects.

Pyrexia attributed to the drug was noted in three cases (1.2 per cent), but others[20] have found a much higher proportion.

In seven additional cases (2.8 per cent) the drug was stopped because of a precipitate drop in hemoglobin. These patients recovered upon the administration of hematinics without resorting to transfusions. We encountered no cases of severe leucopenia, granulocytopenia, or jaundice. Twenty-two cases (8.98 per cent) showed a gradual drop in hemoglobin of 20 per cent or more. French,[21] in analyzing her series, found no appreciable effect of sulfanilamide on hemoglobin when compared with a control group.

The undesirable effects of sulfanilamide were not alarming in any instance although they were encountered in a considerable proportion of our cases. Simple cessation of chemotherapy resulted in the recession of any toxic manifestation.

Worthy of note is the infrequent incidence of serum reactions following the administration of a commercial antitoxin (Lederle) in 111 cases. There were only four (3.6 per cent) instances of serum disease, and these were mild, manifested by urticaria and fever, occurring on the tenth to the seventeenth day.

SUMMARY

1. A series of 680 patients treated at Kingston Avenue Hospital in the spring of 1940 is reported. The cases are divided into mild, moderate, and severe groups. None of the last is included as only three such cases were encountered.

2. In the mild group of cases the controls showed a complication rate of 33.3 per cent, and the sulfanilamide treated cases, 13.1 per cent. The isolation period in the control cases (24.25 days) was longer than that in the treated cases (22.87 days).

3. In the moderate group of cases both the control cases and those treated with scarlet fever antitoxin alone had appreciably larger complication rates (60.3 per cent and 41.5 per cent) than those treated with sulfanilamide alone (24.1 per cent) or in combination with antitoxin (23.8 per cent). The isolation period in the control group (29.7 days) was appreciably longer than that in the three treated groups (25.5 days).

4. The incidence of toxic manifestations from sulfanilamide was 20 per cent, of which 71 per cent were cutaneous eruptions. These were all morbilliform in character, and 57 per cent of them appeared on the tenth day of chemotherapy.

5. None of the more serious ill effects of sulfanilamide was encountered.

6. Of 111 patients receiving scarlet fever antitoxin, only four (3.6 per cent) exhibited serum disease—all mild in severity.

CONCLUSIONS

1. The use of sulfanilamide in scarlet fever reduces the incidence (and severity) of complications.

2. Scarlet fever antitoxin has a beneficial effect on the toxic phase of scarlet fever by reducing the length of the febrile period to a greater extent than sulfanilamide. It is not so efficient as sulfanilamide in reducing the incidence of complications. The combination of scarlet fever antitoxin and sulfanilamide apparently offers better results than sulfanilamide or scarlet fever antitoxin alone.

3. The toxic effects of sulfanilamide are not of sufficient gravity to militate against its routine use in scarlet fever.

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EHLERS-DANLOS SYNDROME WITH A DISTURBANCE OF CREATINE METABOLISM

Report of a Case

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THE Ehlers-Danlos syndrome as first described by Ehlers in 1899 before the Danish Dermatological Society shows three distinguishing features, (a) friability of the skin and blood vessels (dermatorrhexis), (b) overelasticity of the skin (dermatocholasis), and (c) overelasticity of the joints (arthrocholasis). In some instances, additional evidence of pseudotumors and subcutaneous nodules have been noted. The former occur in places of repeated trauma, such as over the Achilles tendon, and are thought to be due to repeated extravasations of blood. The latter are due to small areas of fat necrosis in subcutaneous tissue. These features have been thoroughly described by Tobias.[5]

Several cases of this syndrome have recently been reported in the American literature,[1, 2, 5, 7, 8] but the outstanding complaint of weakness in this patient prompted an attempt to study his muscle metabolism.

CASE REPORT

A 10-year-old boy was admitted to the Babies Ward of the New York Post-Graduate Hospital on Oct. 16, 1939, because of easy fatigability and bruising and a fragile skin. At the age of 2 years the parents had noted that the child bruised after apparently slight trauma, and since 4 years of age he had suffered gaping skin wounds after seemingly minor injuries. Several of these required medical attention, but there was no abnormal bleeding, even after a tonsillectomy at 5 years.

He had a normal birth but developed slowly, sitting first at 1 year and standing at 18 months. Since beginning to walk, he stumbled frequently, and preferred to sit down at frequent intervals, in contrast to his brothers who were very active. The boy stated that he could walk up only one flight of stairs without resting and was never able to run upstairs. He played with younger and weaker boys because he was unable to compete with those his own size. He suffered some dyspnea but no edema, and there was no cardiac history.

Family History.—The father, a 38-year-old Italian, is living and well. The mother, a 37-year-old Hebrew, is also living and well but had thyroidectomy for Graves' disease.

There are four brothers, from 2½ to 19 years of age, who are all normal. No members of the family are known to show any of the signs of this syndrome. There is no history of familial disease.

Past History.—The delivery was full-term and spontaneous. Birth weight was 11½ pounds. The neonatal period was normal. The patient was breast fed for one year and since then has been on an adequate diet. His development was somewhat slow. He sat at 1 year, had teeth at 1 year, and talked at 1½ years. He is now in the fifth year at school in the upper third of his class.

He has had measles, mumps, and chicken pox. He had bronchopneumonia at 1 year and now has frequent colds. He had no operations except tonsillectomy at 5 years.

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Physical Examination.—Weight was 88¾ pounds. The patient was a well-developed and nourished 10-year-old boy with a putty-like appearance. His skin showed numerous thin, wrinkled, pigmented scars which suggested tissue paper on palpation. These were especially prominent over the knees, forelegs, forehead, and chin.

Fig. 1.—Showing the overelasticity of the skin.

Fig. 2.—Numerous thin and pigmented scars are present over both legs.

The subcutaneous tissue was depleted and gave a doughy sensation to the touch. The skin was easily stretched 2 to 3 inches and returned immediately to its former position. This was most evident on the arms, legs, and face. Several fresh ecchymotic areas were present on the thighs and left arm.

The extremities showed a third degree pes planus with hyperextensibility of all the small joints, although not of the knees or elbows.

The eyes, ears, nose, and throat were normal as were the fundi to a very thorough examination. The lungs were clear. The heart was of normal size with a soft apical systolic murmur. Blood pressure was 104/66. The abdomen was negative. Neurological examination revealed a generalized hypotonia with barely perceptible biceps and triceps reflexes, but otherwise normal motor and sensory findings.

Fig. 3.—The hyperextensibility of the small joints is easily demonstrable.

Laboratory.—Laboratory work was quite extensive but will be reported in full. Wassermann, Schick, and Mantoux (1:10,000) tests were negative.

Red blood cells were 3,960,000; hemoglobin, 12.7 Gm.; white blood cells, 6,600; polymorphonuclear cells, 66 per cent; eosinophiles, 4 per cent; and lymphocytes, 44 per cent; platelets, 240,000; bleeding time, 4 minutes; clotting time, 5½ to 7 minutes; capillary fragility (Rumpel-Leede), five petechiae.

Vitamin C saturation showed 330 mg./5 hr. urine with a blood plasma level of 0.26 mg. per cent on Oct. 18, 1939. However, one week later after cevitamic acid therapy, the urine showed 693 mg./5 hr. and the blood plasma, 1.68 mg. per cent.

Blood chemistry showed the following normal values: Urea nitrogen, 16.0; nonprotein nitrogen, 27.0; chlorides, 445; sugar, 65; calcium, 12.0; phosphorus, 5.1; phosphatase, 1.7 units; total proteins, 6.2; albumen, 4.1; globulin, 2.1; sodium, 323 mg. per cent; potassium, 17.0; total lipids, 920; fatty acids, 645; lecithin as phosphorus, 5.1; and cholesterol, 200.

Basal metabolism was minus 10 per cent.

X-ray examinations of the skull, long bones, and chest were negative.

The electrocardiogram showed a moderate left axis deviation.

Electric muscle reactions showed a normal quantitative and qualitative response to faradic and galvanic currents.

Urine samples were negative to routine examinations but on a meat-free diet showed a twenty-four-hour excretion of 0.9 to 1.1 Gm. of creatinine and 0.4 Gm. of creatine with a normal creatinine coefficient (mg./kg. of body weight) of 25. After three months of glycine therapy these values for creatinine and creatine were 1.63 and 0.50 Gm./24 hr., respectively.

The creatine tolerance test after ingestion of 1.32 Gm. of creatine showed a 56 per cent retention after forty-eight hours.

The prostigmine test, as described by Schwab and Viets[4] (2 ampules of prostigmine 1:2,000 and $\frac{1}{150}$ gr. atropine sulfate), failed to produce any increase in muscle power subjectively or as measured on the dynamometer but did cause marked dizziness and abdominal cramps.

Biopsy of the skin showed the stratified squamous epithelium thrown into folds, and stain for elastic tissue showed this to be quite abundant, with some coarse fibers which did not appear to be fragmented. The collagen fibers were not unusual. Muscle biopsy showed striated muscle without change.

In view of the low vitamin C output and the abnormal creatine excretion this boy was put on a high calorie, high vitamin diet and was given 1 dram of glycine three times a day. He was also fitted with proper orthopedic shoes. Although there were no changes in his three cardinal symptoms, he gained 24 pounds in the next six months and was subjectively much stronger. There was no improvement in his dynamometer readings despite progress from a state of barely walking to one in which he could run up a flight of stairs.

Fig. 4.—Elastic tissue stain of the skin showing a few coarse elastic fibers (punch biopsy).

COMMENT

Hypotonia of the skeletal muscles has been noted by Tobias to occur in this syndrome as well as in cutis laxa. In a report by Smith[2] an admission diagnosis of amyotonia congenita was entertained, and Schubert[3] in his case suspected the same condition. A study of this phase of our case did not reveal any definite muscular dystrophy. Blood chemistry, electrical muscle reactions, prostigmine test, and muscle biopsy were all within normal limits. However, creatine excretion was definitely elevated.

As noted recently by Wang,[6] individual creatine excretion varies from day to day and may go as high as 100 mg. per 24 hours in adults. It is also recognized that creatinuria occurs normally in children before the

onset of puberty, although these values too are usually given as below 100 mg. Shelton and Tager,[9] in a study of thirteen normal boys of ages varying from 5 to 11 years, found a variation of 45 to 277 mg. of creatine in urine per 24 hours. Our patient consistently showed over 400 mg. per 24 hours; this is definitely abnormal even for a child.

Wang has also shown that an elevated creatine excretion occurs in phlebitis, although at the time of these determinations there was no external evidence of this condition. At a later date the patient developed an area of superficial phlebitis over the calf of his right leg. Other conditions known to produce creatinuria, such as fever, cachexia, hyperthyroidism, diabetes, and trichinosis have been eliminated.

In the absence of other pathologic conditions, the elevated creatinuria in conjunction with extreme muscular weakness points to some disturbance of muscle metabolism. In this single instance the administration of glycine seemed to have a remarkable effect. Although persons with cutis laxa can look forward to a normal life span, the fact that weakness is an occasional and sometimes major complaint would seem to warrant further investigation of this phase of their metabolism.

Blood studies also failed to reveal any reason, other than friability of the blood vessels, for the tendency to bruising that is characteristic of these patients. Rambar's[8] case was found to be on a vitamin C deficient diet, and this boy showed a definite deficiency as measured by the five-hour vitamin C saturation test. However, intensive cevitamic acid therapy with return of these values to normal failed to influence this purpuric manifestation. Complete blood counts including platelets, bleeding and clotting times, and capillary fragility were all within normal limits.

As in other reported cases, the usual laboratory procedures were found to be normal, although Ronchese[7] reported positive Mantoux tests in two of three cases, and Rambar[8] cited a case of Sezary in an adult with pulmonary tuberculosis.

The etiology of this syndrome still remains obscure, and in the absence of any complete autopsy reports the best explanation available seems to be a congenital metabolic anomaly.

SUMMARY

A case of the Ehlers-Danlos syndrome is presented in which there was an abnormal creatine metabolism. There were, however, insufficient additional findings to warrant a definite diagnosis as to its cause.

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A VACUUM SEAL FOR PRESERVATION OF FEEDING FORMULAS

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THE principle of the vacuum seal[1, 2] has been utilized for a simple arrangement which permits sterilization and subsequent preservation of nippled bottles containing feeding formulas. The device* is a flanged pyrex brand cap (Fig. 1) which fits snugly over the base of the nipple. A small hole in the side wall of the cap is covered with a thin rubber collar which serves as an escape valve.

The formula is mixed at room temperature and added to the bottles which are then covered with the rubber nipples in the usual manner. The glass cap is forced over the nipple rim, and the batch of bottles is sterilized for fifteen minutes at atmospheric pressure. The vacuum produced during cooling may be maintained for several weeks if necessary. When the formula is ready to be used, the vacuum is broken by removing the rubber collar and glass cap.

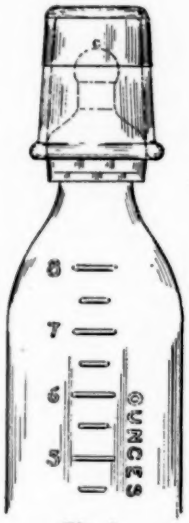

Fig. 1.

Formulas made from whole cow's milk may be preserved without evidence of change in physical properties for several days. Canned milk formulas may be preserved for at least one week at room temperature without evidence of spoilage.

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From the Medical Laboratory, Massachusetts General Hospital.
*Manufactured by Macalaster-Bicknell Company, Cambridge, Mass.

THE TIMID, DEPENDENT CHILD

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A NUMBER of theories have been offered to explain why children are timid. The most facile and the least helpful of these is the concept of heredity. The statement that timid children are born timid is neither enlightening nor melioristic. Timidity, like criminality, is a way of behaving and cannot be considered as being inherited as if it were a Mendelian or unit character. Attempts to utilize the concept of constitution in terms of endocrine secretion or body configuration have met with scant success. Most investigators would agree with Kanner[1] that such classifications have been of no practical aid in working with children.

Not infrequently hypotheses which had been developed under rigid laboratory conditions have been applied to the everyday behavior of timid children. Thus Pavlov's study of the conditioned reflex was seized upon by Watson[2] as the best possible analogy of what actually occurred in the training of the timid child. Present-day psychologic theory is more restrained in its evaluation of this broad principle. Allport[3] spoke of it as being "crudely formulated, and too coarse for precise application in the field of personality," while Jersild and Holmes[4] referred to conditioning as "a decided oversimplification of what occurs in daily life." The same criticism could be leveled at the traditional concept of habit formation with its dictum that repetition fixes any form of behavior because of the resulting "deepened brain pathways." In this respect it is of interest to recall William James' comment concerning these hypothetical brain changes: "All this is vague to the last degree, and amounts to little more than saying that a new path may be formed by the sort of chances that in nervous material are likely to occur."[5]

Although the psychoanalytic emphasis upon psychic determinism has replaced the concept of chance pathway formation, there has been a growing dissatisfaction with its mechanistic and instinctualistic theories, which reached a climax in the stereotyped, dogmatic statements of Klein.[6] In order to supplement this pseudobiologic (instinctual) point of view, Horney[7] presented an environmental (sociologic) explanation of dependent, timid behavior in terms of a potentially hostile world, which is "unreliable and unfair" to the child, and in terms of a consequent overconformity to the standards of others. Horney was of the opinion that the timid child's need for satisfaction and safety results in

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warped spontaneity, a precarious security, and a never-vanishing fear of being deserted. Alexander[8] has criticized Horney's sociologic thesis as being one-sided and in its place has offered (1) the biologic helplessness of the child and his vulnerability to parental repudiation, (2) the frustration of subjective needs resulting from the gratification of certain forbidden impulses, which are considered as threats since they are in conflict with parental standards, and (3) that this frustration provokes hostile impulses which lead to a fear of retaliation.

In keeping with this outline, Despert[9] and Levy[10, 11] have made the release of hostility the sine qua non of their therapeutic endeavors.

Since 1933 the author has given more than 500 children an opportunity to express themselves in thousands of experimental and therapeutic play-situations. Gradually the method of the play-interview was evolved and included as part of the postgraduate instruction at the children's psychiatric service which is conducted by Dr. Leo Kanner at the Harriet Lane Home, Johns Hopkins Hospital. During the past eight years a number of clinical problems have been investigated[12-20] and two of the author's pupils have adapted the procedure for use in child guidance clinics (Solomon[21, 22]) and in the treatment of the juvenile delinquent (Waterman[23]).

The technical arrangements have been described in detail in previous publications.[13, 14, 20] Briefly, the method of the play-interview permits the timid child to view himself objectively while speaking for each of a number of doll-characters, and simultaneously to bring together, for the first time, previously unrelated experiences. There is a unique quality to this type of spontaneity which reveals the patient to himself and helps to remove the need for self-deception. It includes a dynamic interplay of projected personal relationships which disclose essential motivations that can be accepted by the child as his own truth, himself in action. The method of the play-interview does not replace, but rather supplements, basic child guidance procedures by providing a wealth of personal material within a brief space of time. Kanner[24] has pointed out that "this combination of work with the child, the family, the school, and if necessary, the social agencies on behalf of the child gives reasonable assurance that the life situation will, to the extent possible, be made comfortable for the child."

The parent usually is interviewed just before the patient is seen. The timid child accepts this parent-physician-patient relationship as a natural procedure. He is aware that one of the functions and perogatives of a parent is to criticize and is all the more grateful when the physician does not refer to the parental "bill of complaints," but on the contrary, compliments him on his cleverness in "learning his lessons" when the child expresses himself in the play-interview. In contrast to the method of Anna Freud,[25] who seeks to win the child's affection away from the parent, and the procedure of Klein,[6] who makes the

treatment a private matter between the child and herself, the author welcomes the parent as an ally and collaborator. The parent, usually the mother, is given an opportunity to tell her side of the story and also is praised for doing her best in the light of her present understanding. Not infrequently the parent is invited into the playroom while the child reviews what he has learned, and both the younger and the "older, frightened child" (to use Greig's apt phrase[26]) are treated together.

The realization, on the part of the child, that he is being commended from the very start for presenting his point of view concerning his perfectionistic mother, his envied sibling, or his undemonstrative father is accompanied by an immediate sense of self-satisfaction and an awareness that he has found a friend with whom he is able to converse freely.

During the time set aside for the play-interview, random play is almost entirely eliminated. The child quickly realizes that he has not come to play or to be entertained, but to participate as an equal, who has something to contribute as well as to learn. A sufficient interval (one or more weeks) usually elapses between play-interviews during which the child can "digest" his therapeutic experiences, and report what he has been able to *do* with that which he has learned in the play-interviews. This spacing of interviews helps to minimize the child's reluctance to return for subsequent sessions. The physician plays many roles during the play-interview. He may speak directly or for one of the dolls in order to inquire why another doll character acted in the way it did; he may represent the "voice of experience," or he may introduce a humorous twist into the conversation, which tends to make the play-interview an enjoyable as well as a helpful occasion.

CLINICAL PRESENTATION

The first case illustrates the value of a parental "bill of complaints" as well as what occurs when a child is overwhelmed by the criticism of many adults. It also emphasizes the difference between the concept of habit and the human capacity for an immediate reshuffling of perspectives under certain conditions.

Alice was 7 years old (I.Q. 99) when she was first brought to the clinic (Nov. 21, 1935) by her mother with the following complaints: "She gets sick on a street car and bites her nails. She is backward. She doesn't put up her hand to ask questions in school because she thinks what she is going to say is wrong. She doesn't seem to stand up for herself and doesn't fight. She never seems to be the leader. They seem to make her the goat. Of course she is the only child in a house where there are seven adults (parents, paternal grandparents, and three paternal uncles). She takes everything in, the way my in-laws criticize me on the way I train her. They expect her to sit on a chair and fold her hands. They say I am too strict and yet they punish her for less."

The father was described as being undemonstrative but "very lenient" with Alice, and the mother said that he "calls me down when I call her down. He only sees her at night. I get the full blame for everything." The parents were interviewed and discussed a plan to establish a separate residence which never materialized. There was an interval of two years and eight months (July 18, 1938) before

the patient returned to the clinic. The mother's report at this time was that, "She is still shy. She can't take up for herself. She won't go anywhere alone. She has said that she doesn't want to be alone at night. I think it's because there is so much talk of kidnappers. She still complains that she might get sick on the street car."

Apparently Alice had not outgrown her timidity, rather it had grown on her as a way of life. Because of the author's special interest in the problem of the carsick child, this topic was studied during the first play-interview.

A girl doll was placed in a toy street car, and Alice discussed this doll's feelings while riding in the car. She spoke of anticipating an accident and said that this was her "imagination," and that she had been scaring herself. The street car was removed, and a toy bed containing a girl doll was placed before Alice. She went on to discuss the doll's fear of being kidnapped and was able to say that she (the girl doll) "makes it true, but it is not true. She makes it up herself." During the same session Alice selected a colored male doll to represent the kidnapper and said that the girl doll recognized her father when the kidnapper removed his "mask."

She then spoke for each of two dolls as each was indicated by the physician, saying:

Doll A: I told you not to be afraid.
Doll B: I'll remember that now I know it's my father.
Doll A: Yes, I know.
Doll B: I know it's him, and I am not afraid.
Physician: Why?
Alice: She really loves him (All this is?) Her dreaming (and) She loves her father and wants him to love her (and) take her with him. (How does she do that?) She dreams that he is a kidnapper and wants to go with him.

Alice went on to discuss her attitude to her "real" father, saying that he had never kissed her, and added, "I believe my father doesn't love me." The physician asked, "What did you learn today?" and Alice replied, "My father is the kidnapper in the dream, and I think he is the kidnapper because he doesn't love me. That's why I am afraid."

The patient then re-enacted how the girl doll's mother was hurt in a street car accident and said, "Sometimes I think that if we bumped into something it would crash into her (the mother's) side and kill her. (And then?) I'd have my father to go to. (What good is that?) I want him to love me. (It's the same as?) The kidnapper. (Why?) I'd be with my father and he'd love me. . . . (So she thinks?) That if her mother is killed her father would love her. If there was an accident her mother would be killed. (All this is whose idea) Mine. (Why?) Because I am thinking about it in the street car and in bed.

The physician then said, "Now you can ride in the street car and sleep without being afraid. Why?" Alice replied, "It's all in my own mind. What I am thinking of."

Nine days later (July 27) the mother reported that Alice had ridden on a street car without any complaints and added, "I sent her twice to the drug store, a block away, and she didn't hurry back, and didn't say that she didn't want to go alone. She went more cheerfully." During this session Alice spoke for the dolls again as each was indicated by the physician, saying:

Doll A: I was afraid that someone would be in the room.
Doll B: Well, there's nothing in the room.
Doll A: Then I won't be afraid any more.
Doll B: If you don't think about it, you won't be afraid.
Doll A: I thought a kidnapper would get me and kill my mother.
Doll B: Why did you?

Doll A: It was myself thinking that.

Physician (speaking for Doll B): Suppose it would happen?

Alice (continuing to speak for Doll B): Then you'd be with your father.

Doll A: Yes, that would be right.

Alice terminated the second play-interview by saying, "I won't be afraid to go in a room where there is no light." (Why? What did you learn?) "All this is my idea." In the presence of her mother Alice was complimented on her cleverness in "learning her lessons."

On September 10 (five weeks later) the mother stated: "Alice goes into a room without a light and tells me to close the door if I want to. She doesn't say anything at all about being afraid or about going to the store. Before, she'd take anything off the children. She'd take the blame. Now she says, 'I don't take anything off them any more. I take up for myself.'"

During this third play-interview the patient was given an opportunity to observe herself in action at a make-believe school. She began to appreciate that her timidity in the classroom was associated with her anticipations of failure and criticism, saying:

"I was afraid I'd miss (when I got up to recite) and then I'd get the dickens. The children would make me nervous when they raised their hands. I learned this idea is in her (the girl doll's) mind. (And she is?) Me. (Therefore?) I shouldn't be afraid. It's my own self that makes me afraid."

A month later (Oct. 15, 1938, fourth play-interview) the mother's report was, "I see a big difference in her. She is more forward in mixing with children. She reads better in school and doesn't stumble over the words when the children excite her by raising their hands."

Alice was seen for the fifth time after an interval of six months (April 6, 1939). She had been "getting along good in every way." Her mother observed that "she goes on her own more. She's better with other children, saying her part and not being backward." There were no fears of the dark or complaints of carsickness. "Now," the mother added, "She'll go down the street to get her homework from another girl in her class."

Alice now spoke for the dolls, saying:

Doll A: Are you afraid?

Doll B: No, I am not afraid.

Doll A: I am glad you aren't.

Doll B: I learned if *I* didn't think about it I wouldn't be afraid. I used to think a burglar would come in the window.

Doll B: Why?

Doll B: So I could be with him, with my father, (then) us two could be together . . . I wanted to be with him.

Alice was last interviewed after another interval of two years eight months. She had maintained her capacity for healthy, independent self-expression.

The next case presents the influence of disturbing sibling relationships. It also brings into focus the contrast between the concepts of training by familiarization or conditioning and the human facility for self-scrutiny and re-orientation.

Harry, aged 10 years and 5 months (I.Q. 111), was described by his mother on Dec. 13, 1940, as "being unable to take up for himself. He acts like he is scared all the time. He just lets boys get the best of him without resisting them. He is still jealous of his little brother, aged 3 years. If his brother falls down, Harry says, 'It's good for you,' or he goes out of his way to trip him, so I smack him for it. He is still scared of the dark and afraid of thunderstorms. I still have to leave

the upstairs hall lights on. If I turn them off, he calls me and tells me to put them on.'' Harry was first seen at the clinic on Jan. 4, 1939, because several months previously he had developed attacks of abdominal pain and feelings of being suffocated. A tonsillectomy had been performed the previous September, and three days later a circumcision was done with little change in his fearful behavior. The anxiety attacks had disappeared soon after the first visit to the clinic, but his timidity had remained unchanged when he was brought for further treatment on Dec. 13, 1940, almost two years later.

Harry had been ''babied'' according to the parental account until the baby brother arrived and now openly accused his mother of favoring his sibling. The anxiety attacks had appeared after he had seen a dead neighbor ''laid out.'' This first experience with the death of an acquaintance occurred in May, 1938, and had made a serious impression on the patient as he repeatedly referred to it until his attacks of suffocation began in November, 1938.

Harry was seen after the interview with his mother (Dec. 13, 1940) and was told that the physician had heard ''nice'' things about him. He was then asked if he would like help, and he inquired how the help would be given. Two dolls facing one another were put before him, and he was requested to speak for each doll as it was indicated by the physician.

Harry began by saying:

Doll A: I feel sad.
Doll B: Why?
Doll A: Because my brother got hit.
Doll B: That's bad. I'm sorry, rather.
Doll A: Did he go to the hospital?
Doll B: Yes.
Doll A: Where was he hurt?
Doll B: He broke his arm.
Doll A: How many stitches did he get put in it?
Doll B: Fifteen.
Doll A: That's an awful lot of stitches.

Harry spontaneously went on to describe the length of the hospital stay, the boy doll's worry concerning his brother and his interest in visiting him in the hospital. The physician, speaking for one of the doll characters, interpolated the question: ''You're thinking about?'' Harry replied for a second doll, saying, ''I am always worried about my brother.''

A toy bed with a boy doll in it was placed before the patient. He described the doll's feelings in the dark saying that this boy felt that ''somebody might get him.'' He said that the intruder, whom he represented by another puppet, ''can't take both at one time so he takes the little brother.'' Harry described in great detail how the parents discovered the kidnapping, the sending of a ransom note, and the finding of the baby brother by the police. During this first play-interview the patient also discussed his concern that the boy doll's brother ''might run out in the street and get hit by a car'' and that lightning might strike his brother. For the first time these anticipations were brought together and Harry now could say and realize that ''the big brother (doll) thinks all that and scares himself.'' (What is he doing?) He is making himself worry (and) he is making himself nervous. (Just like?) Myself. The patient was complimented on his astuteness in ''learning his lessons'' and was told, ''Now you can tell your mother that you are ready to put out the light. Can you tell me why?'' Harry replied, ''I learned it was only myself.'' (Doing what?) ''Worrying myself.''

The mother was requested to bring the patient on the following day, when it was learned that he had been able to put out the light by himself. During this second play-interview Harry said, ''He (the boy doll) don't have to worry himself

although he thinks his brother is a nuisance.'' He then described how the boy doll always let his brother precede him in the dark so that anyone lurking there could grab the brother first.

The patient continued to speak for the dolls as each was indicated by the physician, saying:

Doll A: You wanted to be the only boy.
Doll B: Why?
Doll A: So your mother would like you best.
Doll B: His mother only liked his brother.

A week later, during the third session (December 21), the mother reported, ''He is much better. I haven't noticed him being afraid of anything. He goes out more with the boys. He used to be shy about playing with them. Now he acts like any normal boy. He doesn't care if they box him or not. (Before?) He used to come in the house crying. He don't cry like he used to when he is teased.''

Harry summed up his experiences in the following dialogue:

Doll A: I don't worry as much about my brother.
Doll B: Why?
Doll A: Because I learned my lesson at the hospital.
Doll B: That's fine. What did you do at the hospital?
Doll A: I talked for dolls.
Doll B: What did you do that for?
Doll A: Because I was learning not to worry.
Physician (speaking for Doll B): How did you do that?
Doll A: Because the dolls were my brother and my friends.

Harry: He (the boy doll) learned it was himself who worried. He learned if something happened to his brother (if he was kidnapped, struck by lightning, or hit by a car) it was what he (Harry) thought about. (Then?) He would be his mother's only boy.

The patient began to discuss his previous fears of being operated on and of being hit by the boys; in each case he could understand that he had been scaring himself. He stated, ''I feel the boys are friendly now,'' and added that he no longer remained awake thinking about intruders prowling about in the dark.

On January 4 (after a two-week interval, fourth session) the mother reported that ''Harry has been going out in the dark where before he used to be afraid and refuse to go four or five blocks from the house. He used to come in and complain about everybody, now he don't. He don't tease his brother like he used to. He is beginning to sass me.''

When Harry was seen four months later, he was described as ''acting happier, and taking more of an interest in things.'' He was no longer fearful or afraid of expressing himself and was looking forward to many good times with his friends.

Perhaps the most frequent type of environmental pressure in our culture is associated with the child's fear of failing in school. The parent also becomes fearful, irritated, and then frankly disappointed when the child does not progress in his studies. A pet parental ambition may have been thwarted; the happiness of other parents who are in a position to boast of the achievements of their children may rankle. In any event there results a continual barrage of criticism which is poorly concealed under the guise of parental help with lessons.

Hilda, aged 9 years (I.Q. 91), had been corrected repeatedly by her mother in order to keep her from failing in school. The child, who always had tried to please, began to complain of queer feelings in her throat, and became even much more at-

tached to her mother, seldom leaving her side. She had been eating only one meal a day for several months preceding the first interview. In the past, except for her mother's company, Hilda had played alone and had avoided all competitive games. Her two younger sisters, aged 8 and 6, were described as being "regular tomboys" and were doing well in the same private school.

During the first play-interview (June 7, 1940) Hilda spoke for a girl doll saying that she frequently had thought of something happening to her mother and added that, as long as her mother was in danger, she felt compelled to remain at her side. She recalled one dream in which a bad boy tried to shoot her mother and another in which her mother was worried because there were insufficient funds for Hilda to continue to attend the private school. In a second play-interview five days later the patient spoke for a girl doll saying that she was afraid that her mother "might put something in her food to make her sick or die." Hilda was able to say that all this was what the girl doll had thought because her mother had considered her to be a "dummy" and didn't want her around.

The third session, five days later (June 17), contained a discussion of how the mother doll had acted as if she preferred the two sisters to the girl doll who was "dumb" in school. Hilda went on to say that, since the food had been poisoned and the girl doll had refused to eat it, her mother and sister would have eaten the food, become sick, and died. Hilda now was able to say that all this had been her own thinking and that she alone was responsible for such thoughts. At this time it was reported that she was beginning to play more spontaneously and for the first time had dressed in her mother's clothes, making believe that she was a mother. Previously Hilda had expressed the fear that there were germs in the mother's clothes, which she now stated could have killed her mother.

By June 25 (the fourth interview, eighteen days after the first contact), Hilda was playing actively with other children for the first time and "standing up for herself when teased." A girl friend had tried to scare her by telling her that a snake was hiding nearby, but Hilda only laughed. She began to report cheerful dreams in which her teacher presented her with a big book for only a penny and said that this seemed to show that she must be smart and that her teacher really liked her since the book was worth at least a dollar.

Hilda was seen for seven interviews (June 7 to July 26, 1940). School adjustment in keeping with the intellectual limitations of the patient was advised and carried out in this case. The mother also had an opportunity to observe Hilda in the playroom and accepted the situation as it actually was, as well as the part she herself had played.

Seven months later (Feb. 4, 1941) Hilda was reported as being a happy child who was able to express herself at home and at play in a normal manner.

The next case represents another example of intimidation which results from the child's conviction that he is faced with what appears to him to be an impossible task.

John, aged 9 years (I.Q. 114), had been struggling with a reading disability and progressively had lost confidence in himself so that he wept whenever any slight difficulty presented itself and spoke of "never doing anything right." The boys at school called him "sissy" because he was timid about participating in sports. He also felt unwanted at home as his perfectionistic, college-graduate mother was disappointed in his scholastic achievement.

During the first play-interview (Nov. 11, 1939) John said that the boy doll in bed dreamed that he was run over by a train, that the house was on fire, and that a ghost might grab him. He said that the boy doll referred to himself as "dumb" and was able to say that he had been calling himself names. He was complimented on his alertness and returned a week later to discuss his fear of being hurt in

rough games, saying that he had been scaring himself at play as well as in the dark and in school. John spoke for the boy doll whose family "didn't want him" and added that the ghost who was coming to take him away was a way of expressing the same idea.

The mother's report a week later (third play-interview, Nov. 25) contained the statement that "John has been in a very much better mood, in more exuberant spirits. He seems to be having a better time and taking things more normally. He has not burst into tears during the past week. He hurt his hand, but he didn't complain of it any more than the average boy would." John discussed his previous tendency to complain whenever he had been hurt. He arranged a boy doll and his mother and said that the boy doll had wanted his mother "to comfort him" and in this way prove to himself that she still "loved" him.

By December 2 (fourth interview) John was described as "not getting upset when criticized." He had received a scolding from his teacher and could hardly keep from laughing. He used the dolls to express this new attitude to himself, saying:

Doll A: How do you feel?

Doll B: Happy.

Doll A: You used to feel unhappy before you learned not to be scared so easily. I bet you would have cried to your mother.

Doll B: I didn't know any better.

Doll A: What did you learn?

Doll B: Not to cry to my mother and want comfort (and) not to be afraid of the teacher. She wouldn't hurt me anyhow. All she could do would be to keep me in after school.

John said that he felt more like continuing his reading lessons now that he was "happy."

During the sixth session (Dec. 23, 1939), five weeks after the first play-interview, the mother stated: "I don't think there is anything to complain about his sensitivity. He doesn't show any evidence of apprehensiveness. He used to lie awake thinking about what might happen."

A follow-up study a year later revealed that John was still being tutored in reading, but he was playing normally with other boys and behaving as an independent, active child.

Sometimes it is difficult for an outsider to fully evaluate a disturbing parent-child relationship and what seems to be an impossible home situation in terms of the dependent child's specific needs. Only the child himself can tell us what troubles him and what he himself has contributed to the total situation.

Dorothy, aged 13 years 7 months (I.Q. 88), was the seventh of eleven children, whose ages ranged from 25 to 7 years, all of whom had been kept in a constant state of turmoil by their surly, temper-throwing, alcoholic father. The mother, who had developed a chronic anxiety state, reported that the father "storms at Dorothy and curses her. When she asked for another piece of meat on her sandwich, he screamed, 'You little — of a —, you are never satisfied.'" She added that, "Dorothy still is afraid of the dark. She is afraid of strangers. She won't stay in a girl friend's house. She wants to be with me all the time. She always says she cares more for me."

Dorothy had chorea in 1937, and in May, 1938, had been placed in a convalescent home from which she ran away. During the first play-interview (June 17, 1938) Dorothy spoke for a girl doll in bed saying that she was afraid that "someone might climb in the window and grab her." She continued to speak for the dolls, saying:

Doll A: I can't help it. Maybe something is wrong with me, but I am scared to go downstairs.

Doll B: You're crazy. You're an old fraidy cat and scared to do anything in the dark. I'm going downstairs. I don't care what you do.

Physician: All this is whose idea?

Dorothy: This one's. Oh! I am doing the talking, it's my idea.

Physician: Why?

Dorothy: It's just imagination. (That means?) You just think of things. You just imagine things and think that they are true.

Dorothy was complimented on her prompt grasp of the situation.

Three weeks later (July 9) her mother reported, "I think she's improving. She has been sleeping good. She has been going to a girl friend's house and has even slept there. She doesn't hang around me so much, but she still won't go in the dark." Dorothy now stated: "I run out and play with other girls. I didn't want to go out before, I was afraid." (Why?) "I don't know." (Would you like to find out?) "Yes."

A toy bed containing a big girl doll was placed before the patient. Dorothy arranged a number of dolls representing various members of the family and began to speak for each of two dolls as indicated by the physician.

Doll A: What are you dreaming about?

Doll B: I had a terrible dream. I dreamed I was passing a dark alley. Some men took me to a dark place. They were going to torture me; then I woke up.

Doll A: You shouldn't think that or you wouldn't dream that.

Doll B: I don't think that.

Doll A: You must have.

Doll B: I'll tell you the truth. I was thinking that my father punished me and sent me upstairs in the dark so I got scared. (The physician asked, "Why?" and Dorothy continued speaking for the dolls):

Doll A: Someone is going to kidnap her or her little brother. (Why?) Because he is helpless and little and can't help himself.

Doll B: Just because he is helpless doesn't mean they will harm him unless he has a lot of money.

Doll A: I think they will hurt him. He is the baby, and the mother rocks him to sleep and pets him.

Dorothy placed the baby brother doll in the father doll's arms and said, "He holds him and pets him. He feels he is better than the rest of the children. She (the girl doll) feels that because he is a boy and the youngest that they treat him better. My mother says she would rather have all boys than girls."

The patient went on to say that, if her brother were taken away, she would be "petted like the baby after he was gone." Again she stated that all this was her "imagination" and that she had been scaring herself and concluded the interview with the statement, "I know I wanted to be petted like the baby."

Dorothy was seen a week later and for a fourth time after an interval of two months (Sept. 14, 1938). Her mother stated: "She don't have a bit of trouble. She goes to bed by herself and don't holler for me to put the light on. She takes a walk every night. Before she wouldn't go nowhere. Now she can go and stay two or three nights at a girl friend's house. She used to be scared all the time and wouldn't bother with anybody. (Now?) She goes out and plays with her friends."

Dorothy terminated this fourth play-interview with a dialogue which demonstrated the degree of her acceptance of what she had contributed to the development of her previous timidity.

She began by saying:

Doll A: You thought someone would take your little brother.

Doll B: I found it's not true now.

Doll A: What made you think of that?

Doll B: I guess I wanted something to happen to him so I could be the baby.
Doll A: Now you found out you can't be the baby.
Doll B: Soon as I found that out, I didn't think of things like that any more.
Doll A: I am glad I found that out.
Doll B: I am glad, too.
Physician: Who was scaring you?
Dorothy: Myself. (Why?) I wanted to be babied. I wanted Louis (her brother) not to be there, that he would be kidnapped. It was my imagination. (That means?) It was me thinking of it.

Dorothy was seen at the age of 16, after an interval of two and one-half years (Jan. 25, 1941) and was described by her mother and by herself as being normally independent and free of her former fears. Her sisters, aged 21, 19, 12, and the younger brother, now 10 years of age, still were afraid of the dark and timid in expressing themselves in many other ways. The father was the same cantankerous alcoholic, and the family was still being supported by community funds.

SUMMARY

Illustrative case material which demonstrates the development and treatment of timid, dependent children has been presented. The problem of timidity may be viewed as a *potential* way of life, a design for living, which is in keeping with the personal needs of the child, who has been overwhelmed and thwarted in his attempts to live his own life. The child is not only *re*-acting to a difficult life situation, but also actively contributing to it in a manner which leads to an increasing need for self-deception and a diminishing sense of self-esteem.

The dynamic concept which has been presented includes a consideration of the individual in action, his specific experiences, and the particular cultural milieu in which he finds himself. The traditional concepts of heredity, habit, and conditioning have been found to be an oversimplification of the actual facts of life. In contrast to an a priori list of abstract motives which have been ascribed to children in general, or the universal need for a mechanically conceived release of instinctual tensions, the method of the play-interview presents a humanistic and plastic point of view. It is concerned primarily with the timid child as an individual who has a particular need for self-realization and who possesses that faculty which especially distinguishes human beings from the rest of the animal kingdom, the unique talent for observing himself in action and then doing something about his previous patterns of behavior. It is this capacity for self-scrutiny which is utilized and organized for the purpose of a co-operative, clarifying, therapeutic experience.

The entire procedure is immediately oriented toward that which went wrong in the actual life situation. The parent is included as a collaborator, and the child is encouraged to look at what he is doing and to express himself as an equal, who has something of importance to contribute. The result is the prompt disappearance of the need for self-deception and the substitution of the pride of being oneself. The emphasis is placed on the child's *doing* something about his timid behavior rather than just *talking* about it. The goal is not to "make

over," but to restore what was there originally, and to assist the child *in every practical way* in keeping with his concrete needs.

Finally, the method of the play-interview helps the timid child to substitute for an ineffectual, fearful, dependent way of life, which he soon finds to be of no value to him, an effectual, spontaneous independent way of doing things. It is this resulting alteration in the person in action or personality which makes it possible for the child to continue to enjoy his newly won freedom of self-expression in thought, feeling, and action.

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Critical Review

POLIOMYELITIS

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GENERAL INTRODUCTION

TO UNDERSTAND a disease about which little is known, it is sometimes necessary to theorize from a few facts and to postulate axioms which become tenable only if they agree with clinical experience. It might be believed that such thinking may result in shrewd guesses, especially if the axioms suggested prove plausible and possibly correct. Such conclusions may often be reached with a minimum amount of visible effort, a condition anathema to the rabid experimentalist who may report or applaud work which shows a maximum amount of experimental effort, but which reveals a minimum amount of thought.

There has been a vast amount of research in poliomyelitis. Most of the experiments have been done on *M. rhesus* monkeys, animals not susceptible to this disease. Much of the information obtained has at times been diametrically opposed to clinical experience and simple logic. This has not troubled some experimenters who at times discard the obvious as unreasonable and enhance the unreasonable because not obvious and because supported by authorities. The only way to test any theory about a human disease is to test it against clinical experience.

PECULIARITIES OF THE POLIOMYELITIS VIRUS

To begin with, it has been suggested that the virus of poliomyelitis has almost an obligate affinity for gray fibers of the nervous system.[1] This conception is not novel, since it has been known that poliomyelitis virus does not remain long in white fibered or medullated tissue; that it is easily absorbed by gray fibered nerves, olfactory, etc., or the gray fibered axis-cylinders of medullated nerves; and that it is found in gray fibered areas.

It has been stated that the virus does not readily multiply in the higher regions of the central nervous system; that the cerebral cortex is not a favorable site for development or even of preservation of the virus.[2] Levaditi[3] states that the central nervous system, particularly the gray matter of the cord, is the principal reservoir of the virus. The very term poliomyelitis is significant—*polio*, gray, and *myelitis*, an inflammation of the gray matter.

Virus could not be absorbed in the human being by way of the many artificial pathways used to produce the disease in the experimental animal. It probably could be absorbed only by peripheral and superficially placed gray end fibers of somatic or autonomic nerves. Its spread would be along the axis-cylinders toward the central nervous system, and it would usually cause damage only when it reached the nerve cell.

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Virus can be absorbed peripherally from only two places: (1) through the skin, or (2) through the gastrointestinal tract. The former has sharpened its ability to react to external stimuli. The integument has come to serve as a protective covering. It prevents noxious elements in the external environment from entering the host. No longer do we actually surround and absorb food as do many animals of the lower orders. No longer does the skin act as an organ of absorption. Only to a minor degree does it even retain the properties of respiration, excretion, and secretion. Biologically, it has become equipped with a specialized defense mechanism with epidermis, hair, nails, etc.—the exoskeleton comparable to the protective coverings of the invertebrates.

It may be asked, "What has this to do with poliomyelitis?" The connection becomes obvious if it is conceded that virus has an obligate affinity for gray fibers. The somatic peripheral nerves are medullated; they possess a myelin sheath and travel thus encased and protected through mesodermic tissues until reaching the dermis, where they shed their coverings and ramify peripherally in the dermis as gray unmedullated end fibers. There they stop. They do not extend through the epidermis. It then becomes obvious why absorption of poliomyelitis virus does not easily take place through the epidermis and why subcutaneous injections are not always successful.[4] Nature has provided a nerveless protective coating, a horny covering or epidermis which prevents virus from spreading to the dermis where the gray fibers and peripheral nerves are found; thus, the spread of the virus through the skin under natural circumstances is prevented, and since gray nerve fibers and virus do not become approximated, the disease is not produced. The skin is a poor experimental portal of entry unless virus is injected intradermally, thereby theoretically contacting the naked gray fibers; experimentally the disease is easily produced when virus is injected here.[5] This confirms the experience and the experiments which tend to rule out biting insects as transmitters of the disease.

The gastrointestinal tract is also an external organ, actually and embryologically speaking, although at birth it is contained wholly within the body. Since it is inside the body, it is not exposed as is the skin and its need for protection is less. Since its functions have followed other lines, it has no need for a protective covering.

There is no external layer in the intestine, no epimucosa to prevent absorption, and it should occur any place along the intestinal tract but more easily and more commonly from the mid-gut and hind-gut. The host is protected against a noxious agent by immune, mechanical, or chemical methods or means. If there is absorption of poliomyelitis virus, and the patient remains well, the protection may be immunologic or chemical in character. If one should have the disease and recover, immunity must have developed. The virus may not be absorbed in some, but it may be irritating enough to cause contractions of the gut, causing the contents to be rushed forward by peristaltic waves, to be excreted before absorption can occur or before there can be approximation of agent and nerve. (This occurs when virus is injected into the gut of a normal rabbit or monkey.[6]) In others, there may be local absorption of material from the gut with mobilization or paralysis of the intestines, which, as every clinician knows, may occur in human poliomyelitis as evidenced by obstinate constipation. In still others, the virus may act as a noxious agent that may be neutralized by some chemical found in the contents

of the normal gut, by the dihydrocholesterols, for example, common detoxifiers, or by enzymes; or, finally, the virus may not be virulent per se and in certain instances may become so only when it is combined with the toxins produced in a stased gut. Thus, there are many reasons why poliomyelitis virus may or may not produce disease—lack of virulence, immunity of the patient, excretion of virus before absorption occurs, or its neutralization in the gastrointestinal tract chemically or immunologically.

Although in the human being, absorption of virus occurs naturally only in those places in the body where naked axis-cylinders or gray fibered nerves come in contact with the virus, a "take" or the successful production of the disease depends upon an unbroken connection between the peripheral absorbing axis-cylinders and the central nervous system.

There are innumerable portals which are employed for the introduction of "takes" in the experimental animal—the sciatic nerve,[7, 8, 9] the cerebrum, the peritoneum,[10] the spinal cord, the eye,[11] the tonsil,[12] the taste buds and the seventh nerve,[13] the vagus nerve,[14] etc. No matter what the avenues, the principle is the same: the virus must be injected some place where it comes in contact with naked gray fibers or axis-cylinders of medullated nerves. If this is accomplished, it matters little where the injection is made. Therefore, one should not be too astonished at the ingenuity of the human mind which thinks up innumerable portals of entry through which to introduce the virus if he but admits the axiom that virus is absorbed anywhere where it may come in contact with gray fibers of peripheral nerves.

If this is true, then it is equally true that the virus could be absorbed from any part of the body where disease and abnormal conditions have removed the normal protective covering and have made it possible for virus and gray fibers to meet. This is especially true where a break occurs in the skin or mucosa or where inflammation is present. Wherever skin or mucous membrane is destroyed, the frayed edges of peripheral nerves stand exposed. In the denuded area, new vessels form, and with them, new peripheral gray fibers. The stage is set for easy approximation of virus and axis-cylinders. It is small wonder then that a tooth extraction, a tonsil operation,[15, 16, 17] or a flap cut[18] in the skin of an experimental animal will provide fields where virus and nerve fibers can meet, as a result of which disease follows. One should remember, however, that although the virus may be adsorbed from a highly artificial portal of entry, the distance between the periphery and the central nervous system must not be too great; otherwise, the virus may be absorbed, excreted, or destroyed long before it reaches the cord. Thus, rapidity of absorption, the speed and ease of transmission, the virulence of the virus, the condition of the neurones, etc., are factors which modify the pathogenesis of the disease.

PLACES FROM WHICH VIRUS MAY BE ABSORBED

Since it is now considered that the blood stream and the lymphatics are not involved in the pathogenesis of the disease, and the intracerebral route is entirely unnatural, it can be concluded that the portal of entry must be somewhere along the gastrointestinal tract, the most obvious areas being either from the upper portion of the gastrointestinal tract, i.e., the stomadeum of the fore-gut, or from the midportion of the hind-gut.

The places where peripheral axis-cylinders are present, and along which absorption could easily occur, are located in the olfactory area, about the taste buds in the tongue (tonsillopharyngeal region), from vagal or sympathetic fiber plexus in the gastrointestinal tract, possibly from the bladder wall, and the respiratory tract.

BASIC CLINICAL AND PATHOLOGIC FACTS

Before proceeding further, let us examine some basic clinical and pathologic facts. The paralyses which occur in the human being are segmental in type and, in the vast majority of cases, they involve the peripheral nerves which have their origin in the lumbar, cervical, and bulbar enlargements, in the order named. Pathologic changes to any great extent are ordinarily found in only three places—in the lumbar and cervical enlargements and, to a lesser degree, in the bulbar area. There are modifications of this general dictum; cranial nerve paralyses may appear without paralysis of the lumbar nerves. On the other hand, the so-called bulbar symptoms may appear clinically during life and yet no evidence of bulbar involvement will be found at death.[19] The cord between these localized areas, i.e., between the lumbar, cervical and bulbar areas, is often free from pathologic reactions, or, if involved, has nothing like that extensive involvement seen in the areas just mentioned. One should remember these areas in the human being, especially when considering experimental paralysis in the monkey (Figs. 1 and 2).

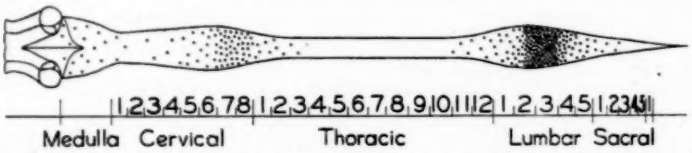

Fig. 1.—Schematic drawing to illustrate the location of pathology in the human being.

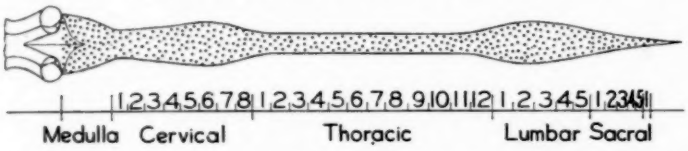

Fig. 2.—Schematic drawing to illustrate the location of pathology in the experimental animal (*M. rhesus*) after intracerebral, intranasal, intrasciatic, etc., injections.

PORTALS OF ENTRY OF POLIOMYELITIS VIRUS

There are two schools of thought regarding the portal of entry. Some believe that (1) the disease enters by way of the nose and others claim that (2) it ordinarily enters by way of the mid-gut or along isolated cranial nerves. The former dictum has been held nearly universally; the latter, until recently, had few remaining advocates save the writer in America[20] and Kling[21] and Lepine[22] in Europe.

A. The Olfactory Portal of Entry:

What evidence is there to support the contention that the olfactory area is the portal of entry? First, let us examine the anatomy of this area.

The olfactory nerves have from twenty to thirty unmyelinated gray fiber olfactory filaments in the region of the cribriform plate. But here

also is the nervus terminalis (cranial nerve XIII) "peripherally hypertrophied in man as compared to the known development in other mammals" (Brookover[23]). The olfactory area contains approximately 1,500 cells of the latter nerve, which with their processes make a vast interlacing network of unmedullated tissue whose fibers *end in the ganglion terminale on the olfactory bulb.* Significant indeed is the assertion made by Brookover that the "grouping of cells and fibers" is "such as might be found in the myenteric or submucous intestinal sympathetic." Most significant is the similarity of the peripheral nervus terminalis to an enteric plexus. The gray end fibers of both the first and thirteenth nerves could take up the virus and absorption could and does take place from here in the experimental animal. One wonders why stress is placed on the olfactory fibers and why the other types of fibers which so closely resemble these found in the mid-gut are ignored and forgotten. But, aside from this, Flexner[24] has stated that the "small olfactory filaments" of the nasal area "are advantageously placed to act as the means of transportation of the virus." The unbroken connection of the olfactory nerve to the central nervous system has been stressed. Flexner and Lewis[25] and others have shown experimentally that absorption may take place from the nasal area, since they reproduced the disease by packing the nasal passages of monkeys with gauze that had been soaked in poliomyelitis virus. All of these conclusions have been confirmed many times, but they merely prove that it is easy to produce poliomyelitis in the experimental animal in this way; such facts do not constitute even prima facie evidence that virus enters the human being by way of this portal. The natural disease never acts like an upper respiratory infection in the experimental animal for no animal gets the disease from another, no matter how intimately exposed.

It is believed that because virus is detected in the nasal washings the nose must be the portal of entry. If such logic is accurate, then the gut must also be a portal of entry because virus is easily detected in the feces.[26-34] It may be said that in the latter case the virus has been swallowed. This, however, does not explain why it is easier to isolate the virus from the gastrointestinal tract than from the nose.[35]

When virus is injected intravenously, it may be found excreted onto the nasal mucosa. It is asserted that it might then be absorbed from this area along olfactory fibers to the central nervous system causing the disease to be produced.[36] Although it is just as logical to suppose that the virus injected intravenously could, like any noxious material, be excreted anywhere along the upper or lower part of the gastrointestinal tract than excreted onto the nasal mucosa only, the dictum can easily be disproved. When the first and thirteenth nerves have been disconnected from the brain and the animals all given virus intravenously, they still get the disease,[37-39] proving that an intact olfactory area is not necessary for the production of the disease when the virus is introduced in this manner.

One would expect to find some pathology in the human olfactory bulb if the disease started here. Smith,[40] however, was the first to stress the fact that there was no evidence of bulb involvement in human autopsy material. This observation was ignored for a while, chiefly because pathology was so easily demonstrated in this area after the virus was introduced intranasally in the experimental animal. Some years later, Sabin[41] examined twenty-five olfactory bulbs from thirteen cases of human poliomyelitis and confirmed Smith's results when he found that

these patients did not reveal the pathologic changes which have been observed in the olfactory bulbs of monkeys succumbing after nasal instillation of poliomyelitis virus. Swan's[42] results as regards the olfactory area were somewhat similar. Sabin and Ward[43] suggested that the results of their "present study [1941] did not support the concept that the olfactory pathway is the portal of entry or exit of the virus." They now feel that the alimentary tract is not only "the probable area of invasion, but also the chief site from which the virus is eliminated."

When the experimental animal is given virulent virus either intranasally or intracerebrally, or even intrasciatically, quadriplegia usually results and usually death. Poliomyelitis is thus produced, but even though this is poliomyelitis, *it is not the kind of poliomyelitis that is seen in the human being.* If the objective is to produce the disease as it appears clinically, then such portals of entry can be excluded.

It is illogical to infer that because the disease is easily produced in an animal by way of the olfactory route this is the probable portal of entry. The ease with which poliomyelitis is produced experimentally in an animal that is naturally immune is no proof that the portal of entry used must be the natural portal of entry in man.

Since the thalamus is the center for effective tone, the area involved in emotions, and the place where effective experiences are intensified,[44] and since a great deal of pathology is found here in the human being and in the experimental animal, and since the olfactory thalamic relay is found in the mesial thalamus, and the formatio reticularis is intimately connected with centers in the hypothalamus and midbrain, and since this in turn is adjacent to or in the direct pathway of the olfactory tracts and there is a direct connection between cord and thalamus via the spinothalamic tract, etc., it has been suggested that most of the early symptoms of the disease—vomiting, drowsiness, restlessness, irritability, fever, generalized hyperesthesia, diarrhea, constipation, anorexia, retention of urine, etc.—probably represent a reaction to irritation as the virus passes by way of the olfactory bulb to the respective centers governing these actions. It is reasonable to assume that if the disease starts in the olfactory area, the areas mentioned previously are involved as the virus passes through the brain stem, and, as a result, the symptoms of the disease should appear here first.

If in the average patient this severe reaction were present in the bulb, there should be more persistent clinical evidence of involvement. Can one imagine that if the severe pathologic lesions seen in human beings at autopsy were present in the early stages of the disease, they would not cause more marked early symptoms? Can one imagine such lesions clearing as quickly as they would have to do in the average patient who recovers? If there is so much or even any pathology present in the bulbar areas in the average case, why do not the symptoms persist? One may say that such a pathologic reaction would appear only in those patients who died. Then the opposite would likewise be true, i.e., that they would not appear in those that live. Curiously enough, it is found at autopsy that they do not even appear in all those who die with bulbar symptoms.

Another objection to the concept that virus passes from the olfactory area to bulb, etc., rises from the fact that serial sections of these very areas in the experimental animal, taken the first few days after the virus is given intranasally or intracerebrally, show nothing more than a possible, slight capillary dilatation even though virus can be recovered from

the areas sectioned. The reactions described in the human being occur relatively late, often long after the early symptoms are forgotten. Nothing that resembles the later pathologic picture is present until symptoms begin to show about the fourth day after injection, at a time when the virus has reached the lumbar area. How can it be explained why the virus, although present, would cause so little damage or clinical reactions on its way through the bulb?

Once virus approximates gray fibers in the nasal area, the hypothetical spread toward the central nervous system can best be appreciated by examining Fig. 3. The virus goes along the olfactory pathways, skips over the synapses to get on a new track, and after passing medulla, pons, and cervical areas of the cord, finally reaches the lumbar enlargement. Specifically, it is thought to pass through the hypothalamus, thalamus, midbrain, and medulla, and then to travel down the spinothalamic tract by single neurones to the posterior column, finally reaching the anterior horn cell area in the lumbar area of the cord.[44] A connection to the dorsal root ganglion by way of Lissauer's tract is thought to bring inflammation to this point. Thus, involvement of either the posterior portion of the cord or dorsal root ganglia might lead to disturbance of pain and temperature sense.

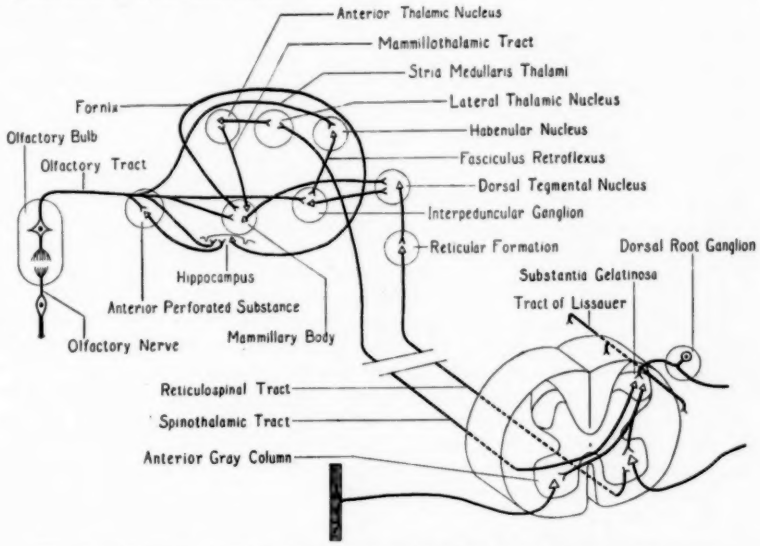

Fig. 3.—Schematic drawing showing possible spread from the olfactory nerve.

If this is the method of spread, then the spinothalamic tract should be involved in every case of poliomyelitis. Immediately it can be asked: "Why don't patients with poliomyelitis have more definite symptoms of spinothalamic involvement?"

The spinothalamic tract carries pain and temperature sense fibers in the lateral column, and touch and pressure in the ventral branch. If the lateral pathway is involved, why not the ventral also? Must we assume an area of anatomic susceptibility and specificity limited only to the lateral branch? It is known that the ventral fibers are not in-

volved in this disease, since touch and pressure are normal. As both fiber tracts run together in the spinal lemniscus and both connect with the thalamus, an almost anatomic predilection for the lateral tract would have to be presupposed to explain the absence of involvement of the ventral fibers, an illogical supposition.

The pain that poliomyelitis patients feel can best be explained by assuming that there is irritation of the somatic nerves prior to the time that the irritant has reached the cord. On clinical examination, it is found that the pain present is not in the skin but occurs in response to deep pressure and is usually limited to those muscles and tendons of muscles that later may become paralyzed. Stimulating the skin by stroking it lightly only occasionally elicits pain. In other words, although the muscle tendons may be painfully hyperesthetic on manipulation, the skin areas that have their nerve supply from the same segment are not hyperesthetic. There is nothing wrong with the *appreciation* of pain in the skin on the part of the average patient. It may well be that pain is caused by the virus as it irritates the sensory neurone of the somatic nerve on its way to the cord, as a result of which occur contraction of the vessels in the muscles and a decrease in the oxygen supply, with anoxemia and pain.

The spinothalamic tract also carries temperature sense fibers. Are there temperature changes which would confirm the impression of spinothalamic involvement? In my clinical experience, the appreciation of temperature has always been normal, although the skin of the leg or arm that is paralyzed may be colder than that of the nonparalyzed member. This, however, is an objective finding and may be easily explained on the basis of vasomotor phenomena secondary to a nerve irritation, such as is seen in many other types of paralyses. Although the skins of the patients whom I have examined were often colder than normal, all of those who were old enough to cooperate could easily tell the difference between heat and cold, even though they felt that the paralyzed areas were cold, an unlikely finding if the lateral spinothalamic tract were consistently involved.

The fact that no plausible reason is given as to why the disease is localized in the lumbar area also casts some doubt on the theory of virus spread from the olfactory area in the human being.

It could be said that ataxia might be the result of irritation of Clarke's column as the virus passes from posterior to anterior horn cells from the spinothalamic tract. Were this the pathogenesis, the virus must always pass from the posterior to the anterior column, and one wonders why ataxia is not more common. Certainly, Clarke's column must always be in the way. But none of our patients ever had acro- or proximoataxia. They always appreciated their position in space. Only an occasional patient had asynergy of movements, somewhat athetoid in type, and sometimes one might even have fibrillary twitchings. The most important point, however, is that these twitchings and tremors, although the rule in the experimental paralyses, were the exception in human beings. This difference may suggest that the pathogenesis of the disease in man and in monkey is different because of the different portals of entry involved.

Why are nerves from the cervical enlargement involved after lumbar paralysis has appeared? Or, still more curious, why is the bulb solely involved at times? Must we deduce that in patients with only bulbar involvement or only seventh nerve palsy, the lumbar motor areas are not

especially sensitive and that the involved motor cells are? Can one explain how the cervical area becomes involved after the virus has already passed through it to reach the lumbar area without doing any damage on its way through the cervical enlargement?

In the majority of human beings and monkeys, paralysis first develops in muscles which receive nerve supply from the lumbar enlargement and only secondarily in those whose nerve supply comes from the cervical area. This is a clinical fact. Those who believe in the olfactory portal of entry have never explained why the virus, in its travels down the spinothalamic tract in the cord, skips the cervical enlargement and, in most instances, involves first the lumbar enlargement and paralyzes *first* the muscles of the legs. Because (1) after intranasal instillation, the virus passes through the brain stem and spinal cord from above downward and because (2) the virus is found present in all levels of the cord just before paralysis appears, it cannot be concluded that this is the route the virus takes in the human being. This is only the route taken after intranasal instillation in the experimental animal, the route taken by a virus which will travel along any axis-cylinder. Must we accept the doctrine of especially sensitive cells? Even this fails us when it is seen that if the virus is injected directly into the lumbar enlargement, there is a delay before the disease is produced.[45]

Must the virus pass all the way through the central nervous system to get to the lumbar area and then trek back to the cervical and pontine areas to involve them later? Or does damage done stay latent everywhere and only reveal itself sooner in the lumbar area? The latter is a possibility; but if it were true, we would expect subsequent or simultaneous involvement of all these areas in every case, which, of course, does not happen clinically.

Recently, Bodian and Howe[46] have stated that the problems involving the portal of entry in poliomyelitis could be approached by methods of experimental neurology and experimental neuropathology, especially since there is no clear-cut evidence of the mode of entrance and dissemination in the central nervous system in man. They believe that their experimental studies have shown that there is a sufficiently close correspondence between the distribution of lesions in the nervous system and the distribution of virus to permit, by histologic examination, a reasonably accurate analysis of the paths of dissemination of the virus. In some of their experiments, the portal of entry employed was the olfactory nerve and, in others, the peripheral nerves. They noted a predominance of lesions in the midbrain as a characteristic phenomenon. When the virus was introduced intranasally, the pathology was present *all the way down* to the lumbar area. The most important thing to remember is that practically all of the motor cells in the anterior horns were involved from the bulb down to the lumbar area (see Fig. 2). They felt that when the virus was injected intrasciatically, intraperitoneally, etc., it entered the spinal cord before it entered the brain; in other words, the virus went up the spinal cord and in its passage destroyed all the motor cells on the way to the bulb, a reversal of the previous process. It is obvious that a definite pathologic picture is produced by the methods used and that the experimenters could tell from the findings at autopsy at which end of the central nervous system the virus had been introduced. But are these facts relevant? Would such findings be the same as those that would be obtained if the virus entered the human being by way of the gastrointestinal tract? Another important point is that the patho-

logic picture seen in the experimental animal where the virus starts from the cerebrum, nose, and peripheral nerves *does not have that distribution* seen in the human. In the latter instance, the pathology is spotty as noted previously. The thoracic area is usually exempt. The pathologic studies, although demonstrating neuronal spread, give no idea as to the method of the propagation of the virus in man. In fact, they demonstrate clearly how the virus could not spread. Nor can conclusions drawn from these experiments be applicable to man, since the localization of pathologic reactions in the experimental animal is totally different (Fig. 3). The thoracic area usually uninvolved in man is the area supplied by thoracic I to lumbar I and from sacral I down. In the experimental animal, the entire spinal cord is involved.

It is stated[46] that the total pathologic picture, including system selectivity, is determined by the differential susceptibility of certain centers based on metabolic or chemical peculiarities, accessibility of virus, and portals of entry. One could agree that the spotty distribution of the pathologic reactions in the human being depends for its existence on the portal of entry; and if the portal is through the gastrointestinal tract, a "take" would depend upon accessibility of gray fibers to virus. But, if one assumes that a virus has an obligate affinity for gray fibers of the sympathetic and parasympathetic nervous systems, the situation becomes clear. One need but know that the virus can be absorbed by gray fibers and can spread from the gut along the sympathetic and parasympathetic nerves to the lumbar, cervical, and bulbar enlargements.

In brief, there is no clinical or even pathologic evidence which demonstrates that the portal of entry in the human being is along the olfactory fibers to the brain.

B. The Gastrointestinal Portal of Entry:

Since 1922, I have taught that on anatomic evidence alone no other logical explanation of the pathogenesis of the disease in man could be made than to consider the portal of entry as being by way of the gastrointestinal tract. For nearly that length of time in the Department of Contagious Diseases, City Hospital, the stools of patients ill with poliomyelitis have been disposed of as are typhoid stools.

In most cases of human poliomyelitis the lower extremities are first affected. Because of this, Wickman and even Harbitz and Scheel first thought that the disease must have its entry through and spread from the gastrointestinal tract. Sicard[47] suggested that the spread to the cord might be by way of the sympathetic nervous system.

Most of those who object to the gastrointestinal tract as the portal of entry mention the studies of Clark, Roberts, and Preston,[48] although the facts presented by them did not rule out this area as a possible entrance of the disease. These workers put virus into the intestines of monkeys that are not naturally susceptible to poliomyelitis, and the disease did not develop. When one realizes that poliomyelitis virus acts like an enzymic catalyst with almost an obligate affinity for gray fibers and that the natural disease can be produced only after the axis-cylinders of the gray fibers have contacted and absorbed the virus, it is easy to understand why these authors did not produce the disease. The axis-cylinders were never contacted; the virus had been swept through the irritated intestinal tract by a succession of peristaltic rushes. However, when the gut becomes atonic and peristalsis is prevented by mechanically dilating the intestines, the virus is brought in contact

with the gray fibers and the experimental disease is easily produced—and it is like that paralysis seen in man.[49]

If the virus involves the autonomic nervous system from the gastrointestinal tract, it might be stated that patients have a peripheral neuritis of the sympathetic and parasympathetic systems, a condition of the autonomic nervous system analogous to peripheral neuritis of the somatic nervous system.

To understand the natural position of gray fibers in the nervous system, some facts must be reviewed. The simplest kind of nervous system consists of afferent and efferent neurones with their axis-cylinders connected with each other by an intercalated, integrated, or connector neurone nerve fiber. In the simple spinal arc of the human being, the fibers that make up the somatic nerves are protected until they reach the periphery, where they lose their myelin sheath and ramify as naked gray fibers in the dermis. In this reflex arc, there is a long sensory nerve component connecting the skin with the posterior horn in the cord; the motor component arises in a cell in the anterior horn and sends its long axis-cylinders from the cord to the periphery. It is important to remember that the connector neurone *lies protected* in the cord between the anterior and posterior horns (Fig. 4).

Fig. 4.—Spinal arc components.

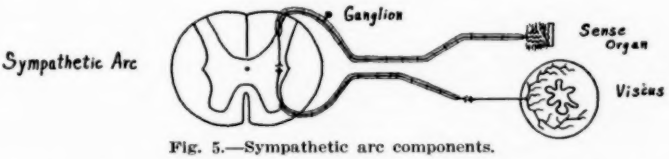

Fig. 5.—Sympathetic arc components.

In the sympathetic nervous system, the axis-cylinder of the sensory neurone (should there be one, and there is for the vascular network) travels from the periphery to the intermediolateral cell column area in the cord where its end connects with the connector neurone, the fibers of which arise in the cord and emerge as medullated nerves, as white rami communicantes. In most instances, except as indicated later, the axis-cylinder travels protected to the sympathetic ganglia, a long distance outside the spinal cord. Thus, at a distance from the cord, arising in the sympathetic ganglia, is the lower motor neurone of the sympathetic nervous system, the analogue of the spinal motor nerve, which in this case is an unmedullated type of nerve which supplies the viscera. It should be stressed that the lower motor neurone of the sympathetic system is unmedullated and its cell of origin *is not in the cord,* but far distant in the sympathetic ganglia. The striking difference between the two nerve arcs, the simple spinal and the sympathetic, is that the connector neurone is found inside the cord in the one and although it arises in the cord in the other, it emerges *from the cord* and runs all the way to the sympathetic ganglion as a medullated connection, except in certain spots (Fig. 5).

The third type of arc is found in the parasympathetic system. Here the sensory neurone runs all the way to the nucleus of origin and the vagus nerve emerges well myelinated. This nerve is actually nothing more than a bundle of connector neurones arising in the central nervous system, the axis-cylinders of which run all the way to the internal organs they supply. The lower motor neurone of this system is but a mesh of plexuses in the walls of the various organs. The connecting neurone here is longer than that of the sympathetic system. In fact, it is almost as long as the lower motor neurone of the simple somatic spinal arc. It should be noted that the peripheral portion of this system, the lower motor neurones of the parasympathetic system, consists mostly of plexuses in the walls of the organs, and these nerves are unmedullated (Fig. 6).

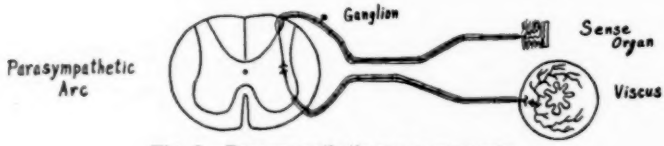

Fig. 6.—Parasympathetic arc components.

If virus would attack only unmedullated nerve fibers and if the portal of entry is the gastrointestinal tract, then it would involve the peripheral fibers of both sympathetic and parasympathetic systems.

If one remembers that the virus of poliomyelitis may have an affinity for gray fibers, he is at once struck with the anatomic fact that the disease usually attacks the nerves which come from those areas lacking white rami communicantes or medullated connections of myelinated fibers, areas located only in the cervical and lumbar enlargements, in those segments from which come the nerves that supply the muscles of the arms and legs. In other words, the somatic nerves to the body musculature possess no direct white nerve fiber connections with the sympathetic nervous system in the areas from the second lumbar down and none upward from the first thoracic segment. Here there are only gray fiber connections and it is in these segments of the cord that involvement occurs. There are medullated connector fibers of the parasympathetic coming from S. II to S. IV. Experimentally the disease can spread by way of the sympathetic nerve supply from the gut to the cord.[49] The spotty spread of the disease can be understood easily if one presages a spread of the virus from the gastrointestinal tract to the lumbar area in the cord by way of the sympathetic gray fibers and somatic nerves of those segments lacking white rami communicantes. With a greater susceptibility or a more virulent virus the spread would be up along the sympathetic collateral chain to the other segments that lack white rami communicantes, i.e., the cervical area (Fig. 7).

That this is not unlikely anatomically is seen from the fact that there is direct unbroken connection from the wall of the intestine to the intermediolateral cell column area in the cord along the sensory sympathetic blood vessel fibers.[50]

Recently, Sabin and Ward have reported their results on human autopsy material.[43] They tested the superior cervical and abdominal

sympathetic ganglia for the presence of poliomyelitis virus in seven patients (five bulbar, two spinobulbar) in whom the virus had been demonstrated elsewhere in the body. They demonstrated that the virus was present in the abdominal sympathetic ganglia of one patient, a patient who died of bulbar poliomyelitis. No virus was demonstrated in any of the others. We have isolated the virus from the sympathetic ganglia of two patients who had spinobulbar involvement. The epidemic last year (1940) was severe in that the virus was potent enough to bridge the synaptic gap of the vagus and produce more than the usual number of cases of bulbar palsy. The presence of virus in the vagus has been demonstrated, for the first time, by us in the nerves of a patient dying with bulbar palsy.[51]

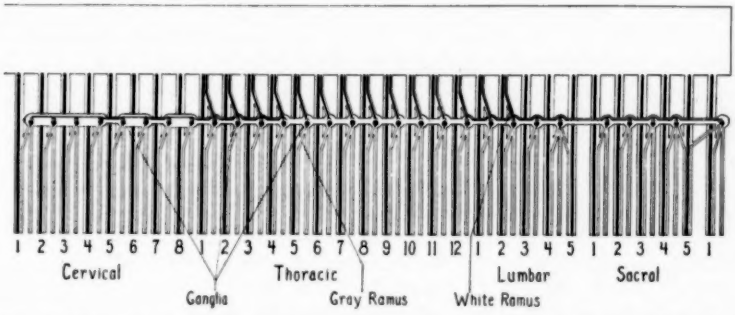

Fig. 7.—Schematic drawing to illustrate position of undefended spaces above T. I and below L. II.

Physiologically, the early reflex changes in this disease could be best explained by assuming an early involvement of the sympathetic nervous system.[52] They are similar to the early reflex changes in typhoid fever.[53] The loss of the abdominal reflex response, followed by hyperactive knee jerks with or without weakness of the quadriceps muscle and succeeded by the loss of the knee jerk reflexes, has its counterpart in physiologic experiments. If sympathetic stimulation increases tone, how would it be affected by thoracolumbar disconnection? The muscles of sympathectomized animals are soon fatigued. Such muscles tire easily when activated, although they may be wholly under voluntary control and still have a simple somatic spinal arc intact. It is reasonable to suggest that the stability of the reflex arc and its ability to withstand fatigue depend, to some extent at least, upon the presence of an integrated sympathetic nervous system. After virus hits the somatic nerve, it irritates it; and when any nerve is continually irritated, it becomes hyperactive and the observer finds hyperactive reflexes. Often, it is impossible to demonstrate these changes because the spread occurs so rapidly. As the virus passes centripetally it reaches the sensory spinal ganglion and produces that curious segmental type of pain that precedes somatic nerve involvement from the same segment. The other type of pain elicited when deep pressure is applied to muscle does not seem to be of central origin. Its presence could easily be explained on the basis of peripheral vasomotor spasm, with decreased blood flow to the muscles and pain on activation.

The virus spread might be compared to the progress of a river flood. The virus spreads along axis-cylinders and spills over in unprotected areas, the greatest damage being done at any break in the defense, in this case, the areas lacking white fibers. Once the virus breaks through, its force is dissipated as it spreads. This may explain the tendency to become spent, and why it does not spread to the lower segments of the cord; or it might be stated that an extensive paralysis of those muscles which have their innervation from the second sacral segment and below will not be seen because the preganglionic medullated fibers arise here. Usually, even the most severely paralyzed patient should be able to move the big toes, and the levator ani, coccygeus, and other perineal muscles should not be affected in the ordinary case. The fingers could likewise be flexed even though the arm muscles should be involved. This is exactly what is seen in the average clinical case. Only when the disease is massive would it involve those segments which have connector fibers (white nerve fibers), the thoracic and abdominal somatic nerves.

This manner of spread would explain the involvement of the lumbar and cervical enlargements, but not bulbar paralysis. The anatomic distinction, but at the same time the connection, is obvious. Virus is absorbed by any gray fibers, whether sympathetic, parasympathetic, sensory, or motor. The unmedullated, gray, and postganglionated fibers of the parasympathetic vagus nerves are located only in the wall of the gut. The vagus nerve itself is chiefly a set of medullated preganglionic connector nerve fibers. Since we have seen that medullated nerves are not too easy to affect, it is understood why all persons with poliomyelitis do not get spreads along both vagi and die because of bulbar palsies. In most instances, the virus is not potent enough to bridge the synaptic gap, but occasionally with a toxic virus it should and does. As the virus reaches the bulb, it would eventually affect the cells of origin. The isolated palsies of the seventh nerve and the bulbar types of involvements are easily understood if one can picture a spread along the chordae tympani, glossopharyngeal fibers, or along local branches of the vagus nerves.

In most instances the initial involvement is in the vagus nerve alone, and it is often incorrectly stated that patients die of bulbar poliomyelitis. A close study of these individuals with so-called bulbar palsies reveals that true bulbar symptoms come on only late in the course of the infection. Occasionally, patients will have an involvement of the vagus nerve nuclei with possible local extension or involvement of some other isolated cranial nerves; or there may be an isolated involvement of the seventh nerve. Long before the clinical evidence of vagal nuclei involvement develops, these patients have a vagus neuritis with dysarthria and dysphagia. They will also have many of the vague symptoms ascribed as being due to involvement of the bulb.

Years ago, Harbitz and Scheel found no evidence of bulbar involvement in cases where symptoms of bulbar poliomyelitis had been noted before necropsy.[19] This becomes clear if it is realized that these patients have a vagus neuritis first and often coincident involvement of the cervical area and are either drowned in their own secretions because they can't cough or expectorate or they are suffocated long before the virus has been able to reach the nerve nuclei in the medulla, and this despite the fact that they have what are termed classical signs of bulbar poliomyelitis.

It matters little to the patient whether he has a peripheral vagal involvement and drowns or suffocates, or has a vagal nuclei involvement and drowns or suffocates. However, the patient with the latter condition rarely lives, while one with the former may survive. This result only confirms the impression of a primary neuritis followed later by nerve nuclei involvement.

There is an orderly progression of signs found in these patients—a curious feeling of tightness in the chest, perhops associated with cardiac irregularities, followed by thickness of speech and a slight inability to swallow, especially heavy foods. Later fluids cannot be swallowed. As the virus extends up the vagus nerve, the pharyngeal reflexes become lost, mucus and secretions collect in the throat, and the patient cannot cough or expectorate. These individuals often die at this stage, the secretions entering the bronchi and drowning them; or virus may extend to and involve the cervical area, and the patient suffocates because the respiratory muscles are involved. If the virus extends up farther, it finally reaches the vagal nuclei and a typical response appears. There are a marked tachycardia and a decrease of the respiratory rate, with deepening and sometimes irregularity. The patient evinces all the signs of vagus escapement. When this condition exists, the patient has an involvement of the dorsal vagal nuclei and the probabilities are that he will die. In these instances pathology will always be found in the bulb.

Were the virus to have a central effect on the bulb from the beginning of the disease, vagus escapement should be commonly found when the illness starts, but since it is found only toward the end of a typical vagus involvement, it is safe to conclude that the condition could not have been present at the onset. It is also logical to believe that practically all deaths due to so-called bulbar involvement are the end result of a disease which started out as a vagus neuritis and that often patients may die of the effects of their vagus neuritis long before they have developed involvement of the vagal nuclei.

The isolated seventh nerve palsies can easily be explained on the same basis. Such paralyses are not uncommon and since these patients rarely die, little pathologic material is available. However, there occasionally may be a concomitant vagal and seventh nerve involvement at times with sixth nerve involvement and paralysis of accommodation as well.

Ordinarily, somatic motor paralyses are thought of in connection with poliomyelitis. We forget the autonomic nervous system. What would happen if the lower motor neurones of both sympathetic and parasympathetic nervous systems became involved? There are local or general paralyses of the gut; gas pockets form as a result and intractable constipation may occur long before any somatic spinal paralysis pain appears, a condition often diagnosed as intestinal flu. In the occasional case, the local stimulus increases peristalsis and causes diarrhea. How can one explain the intestinal involvement which appears before somatic paralyses on the basis of central nerve involvement?

If the lower motor neurone of the sympathetic is involved, the thoracolumbar outflow may be disturbed. Since these nerves supply the sweat glands, experimental evidence may be secured of their involvement experimentally. When pilocarpine is injected into a patient who has one-sided paralyses, there is sweating of the skin over both the paralyzed and nonparalyzed sides.[54] When the specific thoracolumbar stimulant

adrenaline is given later, the sweating ceases on the normal side and still continues over the paralyzed area, demonstrating that the sympathetic fibers are out of order. A similar condition sometimes exists in these patients clinically in that sweating autonomically appears even without the aid of stimulants, and the sweating may be long, profuse, and intractable.

The urinary bladder is often found to be paralyzed and involved before any symptoms of somatic paralysis have appeared anywhere. The urinary paralysis could not be central or cord in origin, since in most instances there is no paralysis of the muscles innervated from the same segment.[55] This paralysis of the bladder usually disappears within from seven to ten days, irrespective of the massiveness of the somatic lesion remaining. Such ready recovery would be impossible were the origin of the lesion in the cord.

The superficial abdominal reflexes are modified. This is not due to an upper motor neurone lesion.[52] The reflex condition occurs even before somatic paralysis comes on. They are also found modified in another gastrointestinal disease, typhoid fever.[53] Like typhoid fever, these reflexes return when the poliomyelitis patient is better.

Is there any evidence that the virus can spread along sympathetic nerve fibers? Monkeys with the spinal cord removed from T. X to L. III, inclusive, leaving the sympathetic as the only connection between the upper and lower parts of the cord, still get the disease, the arms becoming paralyzed if the sciatic nerve is injected, demonstrating that virus can probably spread over the sympathetic nerve fibers. Other animals in which the cords had been similarly excised got the disease when the virus was injected intracerebrally. The virus was found not only in the cord central to the cut, but also in areas caudad, in places where the circulation had not been disturbed, and where the area was still viable.[56]

Other points may be mentioned. When the innervation of the gastrointestinal tract is disturbed, a paralysis occurs much sooner after the intracerebral injection of virus.[57] The disease given experimentally by way of the gastrointestinal tract progresses as quickly in the animal as it does in the human being and is recognizable within twenty-four hours in the spinosomatic nerves when the peripheral nerves are studied between Nicol's prisms. Involvement of the somatic nerves occurs about three to four days after intracerebral injection.[7] After gastrointestinal injection, they are found to be involved within twenty-four hours.[58, 59]

Most of the information about this disease has been deduced by observing animals injected either intracerebrally or intranasally. We have conditioned our minds in terms of these portals of entry. Obviously, specific conclusions regarding pathogenesis, drawn from the results of experiments in which the intracerebral portal was used, can be discarded. The conclusions about pathogenesis made following intranasal injections are questionable. Certainly the explanation of the possible anatomic spread by this portal does not stand critical examination.

The *M. rhesus* monkey is not susceptible to poliomyelitis. It has normal resistance in the gastrointestinal area. However, if this tract were put out of commission or made abnormal, so that the virus could be absorbed and approximate the gray fibers, the disease might be produced naturally. This can be done by making the monkeys rachitic, after which the disease is easily produced by way of the gastrointestinal tract.[60] If

rachitic animals are to be made more susceptible, all that is necessary is to inject them with enteric organisms or toxins. One would deduce that the most vulnerable species of animals to be used would be one that would grow most actively after birth, one presenting an enormous percentage of growth during the first few weeks of life; and it is this very type of animal, the Eastern cotton rat, that has lately been discovered as a proper medium for the production of this disease.[61]

The fact that the glands of the mesentery are enlarged does not imply a general infection, but merely indicates that the area of the intestines which they drain is involved, as would be expected in a stased gut, a local reaction like in typhoid fever.

There are a lymphocytic reaction and a response in the glandular elements that are typically of a typhocoli nature. A distinct leucopenia and a relative lymphocytosis would be the expected result from an infection caused by such a close generic relative of the typhoid organism as the colon or the paratyphoid bacillus. Such a blood picture in poliomyelitis has been described by Müller,[62] Taylor,[63] and Gay and Lucas,[64] although the figures of the latter have not been completely accepted by Peabody, Draper, and Dochez.[65] The most complete and accurate observations on the blood count in experimental poliomyelitis have been made by Harmon, Shaughnessy, and Gordon.[66] They reported that in the stage of prostration there is always a marked drop in the white blood cell count to a point far below the normal for a given animal, a leucopenia with both lymphocytes and polymorphonuclear neutrophilic leucocytes participating. They could not confirm the opinion that a change in lymphocytes with a leucopenia was a characteristic experience in the stage prior to the appearance of paralysis. In most of their experimental animals, there was a preparalytic increase in neutrophilic leucocytes coincident with a rise in body temperature and a corresponding drop in circulating lymphocytes, a drop frequently of sufficient magnitude to mask the leucocytosis when only the total number of white blood cells was observed. An initial transient leucocytosis was noted by these authors within a few days after the injection of the virus. These findings were confirmed in duplicate studies.[67] During the latter stages of the disease, the lymphocytes seem to be withdrawn from circulation. This would fit in well with the advent of local intestinal stasis and the accumulation of intestinal toxins.

Osler's observations that a state of poliomyelitis occurred in typhoid fever with the symptoms of acute ascending paralysis are pertinent to our thesis.[68] Recently, when enteric toxic filtrates were added to old acclimated monkey virus strain, the disease was produced in the cotton rat.[69-72]

Other things suggest the gastrointestinal tract to be the area previously involved in this disease. When morbidity curves of infantile paralysis are considered in relation to the season, it is found that they may be practically superimposed on dysentery curves.[73] Aycock and Eaton[74] have described a spring and summer peak of poliomyelitis morbidity and have noted that the curves occur about the same time as do those for the spring and fall epidemics of typhoid fever. Like typhoid fever, infantile paralysis disappears with the onset of cold weather.

The disease occurs during the typhoid fever season and Kling[75] has claimed to have demonstrated the presence of virus in water. Virus has been found in urban sewage[76-78] (Kling quoted by Paul and Trask[76]),

and infected water might be swallowed in swimming. In this connection, Caverly's[79] and Murphy's[80] observations are interesting. A history of swimming and swallowed water is frequently given to us. As Paul and Trask state, the virus has never been isolated from "running water," but their experiments demonstrate that it can be isolated from "running sewage." In incorporated places in Louisiana with water supply and no sewage disposal, the disease incidence was greater than in those places with good water supply and proper sewage disposal.[81]

The disease has been produced experimentally by way of the gastrointestinal tract. When peristalsis was prevented in the *M. mulatta* monkey by mechanically dilating the intestine and the virus brought in contact with gray nerve fibers by injecting a suspension directly into the gut, the disease was produced.[49] When the virus was introduced into the intestinal wall and contact made with subserosal nerve fibers, the disease was easily produced.[49, 81a, 81b] When monkeys were made rachitic and the virus merely introduced by stomach tube, the disease developed. The important point is that the clinical disease produced was similar to that which appeared in man, i.e., monoplegia, paraplegia, etc., were found. In the few animals examined by us, the pathologic picture was likewise similar to that which appears in man in that the lesions of the experimental disease were limited to the lumbar and cervical enlargements and in one instance to the medullary area.

Trask and Paul[82] were able to infect the green African monkey after feeding food artificially contaminated with virus. The disease has been noticed in nature in a chimpanzee,[82a] and has been produced by way of the gastrointestinal tract in the chimpanzee by Howe and Bodian.[82b]

Sabin and Ward[82c] caused the production of poliomyelitis in *Cynomolgus* monkeys by feeding them contaminated bananas as well as 2 to 4 c.c. of a heavy suspension of virus. Burnet and Jackson[82d] also described similar reactions in *Cynomolgus* monkeys following oral injections. They felt that the spread to the central nervous system was by way of the autonomic nervous system.

THE ROLE OF MEDULLATION AS A BAR TO SPREAD OF THE VIRUS

Myelin seems to be a bar to the spread of the virus. Since the virus does not seem to spread well along medullated nerves, it is plausible to suppose that it may be stopped by the factor which constitutes the only marked difference between gray and white nerve fibers, namely, the myelin.

Conversely, one could deduce that if the myelin is unhealthy the spread of the virus may not be stopped. Theoretically, one might state that the myelin of a normal nerve fiber functions as a colloidal chemical and adsorbs or repels the virus of poliomyelitis. Were this true, a factor in natural protection against the disease would also depend to some extent upon the state of the myelin in the nerves and natural inherent immunity would be partially a question of colloidal balance, with protection in the average case depending on the presence of a sufficient amount of something, perhaps phospholipids, in the myelin, as well as antibodies, etc.

Goodpasture[83] inoculated an encephalitogenic strain of herpes virus into the area supplied by the fifth sensory division. He found that there might be no nervous lesions until a point is reached immediately centrad to the planes where the sheath of Schwann disappears, where the myelin sheath is not sufficiently developed to prevent the escape of virus into the susceptible neuroglial tissue. When the masseter muscle was injected

with the virus it was taken up by the motor branch which has a substantial myelin sheath and the first intracerebral lesions were in the motor ganglion cells of the fifth nerve nucleus, even though the medullated fibers pass through a wide zone of susceptible tissue without evidence of neuroglial involvement. Such a virus spreads like water through a tunnel.

Virus adsorbed or repelled by healthy myelin in normal persons could be in a state of colloidal equilibrium and give little or no symptoms of its presence after injection via the gastrointestinal tract. Certainly, it is difficult to give a monkey the disease by this route if the animal has previously been fed adequate amounts of vitamin D,[84] which produces good myelin. When the myelin is insufficient, the nerves may not be protected.

White fibered or medullated nerve tissue contains about 5 per cent of cholesterol. Gray fibered tissue, which has an affinity for poliomyelitis virus, contains only 0.7 per cent.[85] Could cholesterol act like a colloid and adsorb or in some way inactivate the virus in vitro?

In a few experiments, inconclusive it is true, it would seem that cholesterol, ergosterol, and crystalline vitamin D inactivate suspensions of purified poliomyelitis acclimated monkey virus, although ergosterol, like cholesterol, did not inactivate unpurified poliomyelitis.[86, 87]

In the adrenals, the postganglionic unmedullated fibers are limited to the organ, while practically all of the preganglionic fibers are well medullated up to the capsule of this "abdominal brain." Normal vitamin-D-fed monkeys resist the disease even when the gland is injected, the preganglionic medullated fibers presumably preventing a spread of the virus. However, when the myelin of these medullated nerves was rendered deficient by withholding vitamin D to where the phosphorus content was from 1.2 to 1.5 mg. per 100 ml. of blood, the disease was easily produced when the virus was injected into the organ. Deficient medullation, if such it is, therefore permits a spread of poliomyelitis virus.[88]

When monkeys are made rachitic and their peripheral nerves are ground with virus, the virus is absorbed since the supernate is not infective; on the other hand, when nonrachitic nerves from vitamin-D-fed animals are ground with virus, the virus is not absorbed and the supernate is infective.[88] It may be suggested, therefore, that the spread of poliomyelitis virus to the central nervous system might be stopped by the myelin contained in the sheath which covers the gray fibers.

IS THE VIRUS THE SOLE CAUSE OF THE EXPERIMENTAL OR HUMAN DISEASE OR MERELY THE EXCITING CAUSE?

After intrasciatic, intranasal, or intracerebral introduction of a virulent poliomyelitis virus in monkeys, the disease comes on within four to seven days. When the virus was injected directly into the lumbar cord itself, the animals did not become paralyzed at once, two and one-half days elapsing before this condition was noted. Why should there be such a delay? It is strange indeed that the virus can be absorbed and be present in doses lethal for monkeys in the tissue of the cord, medulla, and even brain long before the production of somatic paralysis in this animal. It argues for the fact that the acclimated monkey virus, although easily absorbed by gray fibers and transmitted to the brain and cord along axonic pathways, does not, in its passage, immediately produce pathologic changes of sufficient intensity to result

in clinical evidence of disease. The virus does not cause demonstrable destruction along its axonal pathway.

Although the virus initiates the disease, there are some clinical and experimental findings which make one wonder whether the virus alone, as it is carried in the laboratories, is the sole cause of infantile paralysis. Other diseases, such as swine influenza[89] and oroya fever,[90] are produced by a combination of factors. Perhaps poliomyelitis also is such an infection.

An accelerated production of the disease may result in the experimental animal when stool or sewage containing the virus is used to start a strain. Once a virus is acclimated, however, its behavior becomes somewhat fixed. This leads one to ask whether there is something lost on acclimation.

More attention was paid to stools, and it was found that those obtained from patients ill with poliomyelitis during the acute stage of poliomyelitis were much more toxic to guinea pigs than those obtained from the same patients during convalescence.[91] Obviously, something had been produced in the stools during the course of the disease that was more toxic to guinea pigs, something that was not present in normal human stools; and yet it was equally obvious that this something was not the virus of poliomyelitis,[91] although it had been neutralized by convalescent poliomyelitis serum.

Stools collected from young normal monkeys were emulsified and injected subcutaneously into guinea pigs; there were but slight local reactions. The stools obtained from the same monkeys after they had had an attack of experimental poliomyelitis were much more toxic to guinea pigs, in some of which the abdominal areas sloughed and some of which died.[92]

It occurred to me that a secondary factor must be present in some patients before the clinical condition of infantile paralysis could be produced. The colon bacillus was considered in this light. The agglutinin titers contained in the blood sera of poliomyelitis patients, taken at the height of the disease and later during convalescence, were compared. It was found that there was a marked difference, since the agglutinin titers of the sera taken at the height of the disease were much less for the enteric group of organisms than they were for those taken during convalescence.[93]

It was not possible to say at first whether the agglutination titer values were lowered with disease and returned to normal with recovery, or whether the titers were lowered before the disease occurred and increased with recovery.

This information had to be supplied experimentally. The young *Macacus mulatta* monkey is very susceptible to poliomyelitis when the virus is injected intracerebrally and has little or no agglutinins in its blood serum against the colon bacillus. As the animal gets older, its serum agglutinin titer for colon organisms becomes higher. Young monkeys were injected intracerebrally with potent poliomyelitis virus. When they contracted the disease the agglutinin titers of their blood sera were found decreased, and immediately before their death the agglutinin titer values were practically nil. From the results found in the human and from those obtained experimentally in monkeys, it may be inferred that the agglutinin titer for the colon group is depressed during the acute stage of poliomyelitis.

The idea that the enteric organisms have some part to play in the production of this disease was further bolstered by the fact that the monkeys which had been actively immunized with enteric organism vaccine had a definite, although incomplete, nonspecific protection, since a longer time interval elapsed before the protected animals contracted the disease.[94]

When enteric organism filtrates are injected into monkeys intracerebrally, there is no effect; virus injected the same way causes the disease to appear within seven days; the injection of virus and enteric organism filtrate into the motor area of the brain causes immediate paralysis of the heterolateral side.[95] Add to this the fact that we have acclimated the Flexner M. V., Philadelphia, and the Toomey strains to the cotton rat by the use of enteric organism filtrate as menstruum, and one must admit that there might be some connection between virus and resident enteric organism filtrates.

Toxins produced in the intestines might be absorbed by and travel over the sympathetic and parasympathetic nerves as far as their cells of origin, conditioning them as it were. Later, in the experimental animal, when the virus would enter the gastrointestinal tract, it might spread directly from the intestines, over the conditioned autonomic nerves to the spinal cord or bulbar areas.

It has occurred to us that the difference in virus strains might be due to the added character supplied by a secondary factor; in this case, the type of organism and its toxin found in the gastrointestinal tract, leaving the pure virus when purified and experimentally acclimated always the same.

THE PATHOLOGY OF POLIOMYELITIS

There has been a great deal of dispute about the pathology of the disease (see discussion[7]). For a long while, it was believed by Flexner and Amoss[96, 97] that the specific causative factor entered the system through the upper respiratory mucous membranes to the olfactory lobes of the brain, from which, by means of the cerebrospinal fluid, it was distributed throughout the substance of the nervous organs. These authors also state that the virus might reach the brain by any nerve channel and with great difficulty from the blood. This theory was supplemented by the one of neuronal spread, first definitely demonstrated by Fairbrother and Hurst.[7, 8, 98] In itself, this was not a new theory, but it was the first definite demonstration of this theory.

For a long while, it was believed that the interstitial reaction and edema occurred first and cell destruction later. The march of events may occur so rapidly in man that the processes will overlap and distinctions are not clear. This probably is the reason why an earlier school thought that edema, etc., caused the death of cells. Schreiber's opinion (quoted by Hurst), expressed in 1911, that there is a direct action on the nerve cell has been borne out by later experience. In any event, the toxic material injures or destroys motor cells, an action which immediately is followed by leucocytosis and neuronophagia. After this the vascular phenomenon may occur: dilatation of pre-existing capillaries; rupture of some local foci of red cells; edema; and finally perivascular infiltration with round cells. Any cell of the cord may be destroyed, including the neuroglial.

SECOND ATTACKS OF THE DISEASE

It has been demonstrated that animals receiving injections of virus either by way of the gastrointestinal tract or intracerebrally may contract the disease again when subsequently given injections of homologous or heterologous virus intracerebrally.[99] Flexner has also called attention to the fact that monkeys might again get the disease.[100, 101] Although later experiments confirmed previous experiences[102,104] in the experimental animal, it is nevertheless believed that once immunity is established in the human being, it is fairly permanent.

TABLE I

POSSIBLE METHOD OF VIRUS SPREAD IN INFANTILE PARALYSIS

PHASE	POSITION OF VIRUS	SYMPTOMS
I	At first the virus is free in the gastrointestinal tract.	There are none; or possibly some with diarrhea and pain.
II	The virus becomes fixed in the unmedullated postganglionic fibers of the thoracolumbar outflow and parasympathetic nervous system and spreads along the sympathetic nerve fibers to the ganglia.	The abdominal reflexes are absent or modified. There may be constipation, indefinite pain in the belly, and pain over the back.
III	The virus spreads from the sympathetic nervous system and reaches the somatic segmental nerve.	In addition to the symptoms described in phase II, there is hyperactivity of the reflexes with tiring on repeated stimulation.
IV	The virus, spreading backward over the somatic segmental nerve, reaches the spinal ganglia.	In addition to the symptoms described in phases II and III, there is segmental pain in the muscles and tendons supplied by nerves of the segments involved.
V	Simultaneously, the virus is absorbed and excreted; enough may accumulate at one time in the urinary bladder to involve the detrusor and sphincter.	A peripheral type of urinary bladder paralysis with overflow dribbling may now appear when the virus factors present are absorbed by the terminal gray nerve fibers of the bladder and its neck, whether of the sympathetic or parasympathetic nervous system.
VI	The virus reaches the cord and involves the anterior horn cell.	In addition to the symptoms described previously, the reflex reactions now become diminished or lost. Muscle paresis or paralysis begins to appear.
VII	The virus travels up the sympathetic nerve chain to involve the cervical area.	Here the train of events is the same as outlined in phases III and VI.
VIII	The virus may be virulent enough to be absorbed directly by the vagus nerve (i.e., the connector fibers in the gastrointestinal tract).	A condition simulating bulbar palsy appears. There is dysphagia, dysarthria, etc.
IX	The virus may be absorbed directly over the chorda tympani, from the pharynx, etc., directly to the nucleus of origin of the cranial nerve in the bulb.	The results are the same as in phase VIII.
X	In the rare instance, the virus may travel along the gray nerve fibers of the autonomic nervous system to the bulb, the internal capsular and the cortical areas.	The symptoms here would depend upon the localization of the virus, with bulbar palsy, hemiplegic and encephalitic reactions.

All second attacks of poliomyelitis reported in the literature have been analyzed. Many cases cannot be considered bona fide second attacks of poliomyelitis. It is probable that if the gastrointestinal tract is considered the portal of entry, this area would be sufficiently immunized after one attack so that subsequent attacks would hardly ever occur.[105]

THE EPIDEMIOLOGY OF POLIOMYELITIS

The epidemiology of the disease is interesting. It appears in our district between July 15 and November 1. These dates coincide with the time when perishable fruits and vegetables begin to ripen. In southern and midsouthern states, epidemics appear earlier than in the Lake border states. Occasionally cases may be seen just before or after the dates mentioned, but the majority of epidemics in our locality start in late summer and early fall, a time which corresponds to the same seasons in which it appears in the other half of the equator—in the south temperate zone, in Australia, New Zealand, and the Argentine Republic.

The histories of these patients have always been interesting. Many date their attacks to a dietary indiscretion such as eating unripe fruit or vegetables, such as apples, pears, peaches, plums, corn, and especially grapes. The handling of infected fruit or vegetables by infected people, the eating of infected fruits and vegetables by cattle, with subsequent infection of milk, and the spreading of the infection from fruit to fruit by flies—all of which occur at the season of greatest plenitude of fruits and vegetables—could serve to explain the spread of the disease and the incidence at this time of the year. If we add this to Kling's conception of water as a possible source of infection, all the factors of the epidemiology of the disease could be explained. One should not believe that the fruits, etc., cause the disease, but they may carry the infection. Thus, contaminated food and milk may provide the greatest source of infection.

POSSIBLE METHOD OF VIRUS SPREAD IN INFANTILE PARALYSIS

What is present objectively in patients ill with poliomyelitis? There is segmental paralysis of muscles, the nerve supply of which comes from the lumbar enlargement; to a lesser extent of the muscles that receive their nerve supply from the cervical enlargement; sometimes of the muscles supplied by the vagus and the seventh nerves; and if the exposure is massive, occasionally of the muscles supplied by the third and sixth nerves or intercostal and abdominal wall nerves. One might construct a chart of pathogenesis (Table I) as well as Fig. 8.

PROPHYLAXIS

Considering prophylaxis in a broad aspect and with the epidemiologic facts in mind and with the idea that the portal of entry is by way of the gastrointestinal tract, it is believed that (1) children should be taught to wash their hands before eating anything, not before every meal, but before eating anything; (2) no milk should be drunk which has not been pasteurized, especially milk obtained during the summer months; (3) no water should be taken unless obtained from an approved source; (4) no unripe fruits or vegetables should be eaten without first having them washed; (5) children should avoid dirty swimming holes and, if possible, should not swallow water while swimming; (6) the bowels should be kept open, especially during the summertime.

THEORY OF DISEASE CAUSATION

A dual condition of immunity may exist against this disease in man. This idea indicates several mechanisms and explanations.

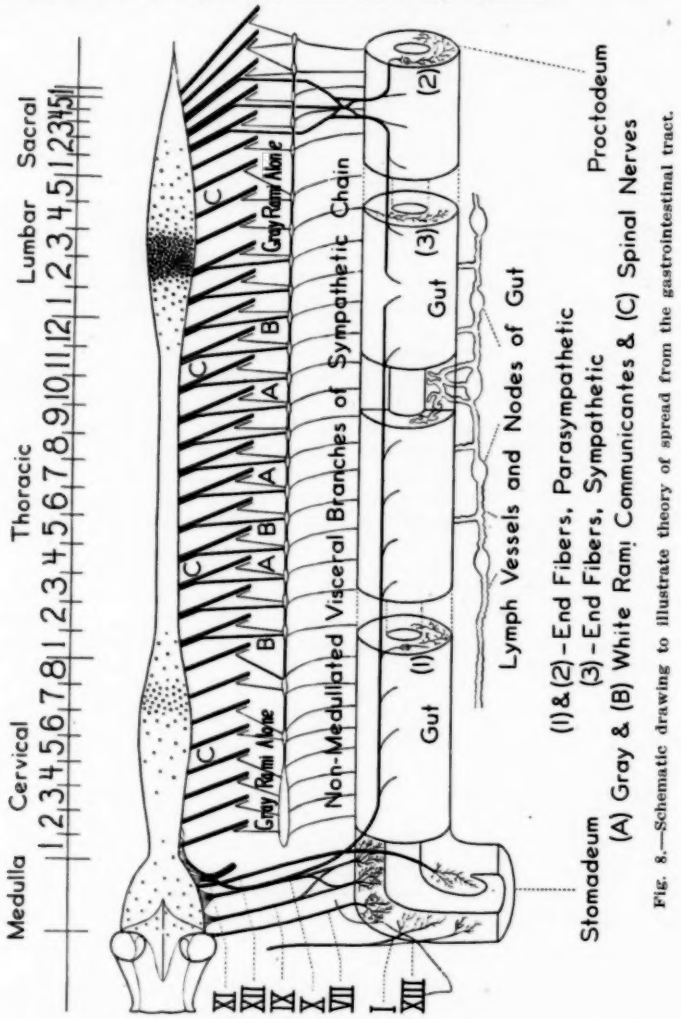
Medulla
Cervical
Thoracic
Lumbar
Sacral
1 2 3 4 5 6 7 8 1 2 3 4 5 6 7 8 9 10 11 12 1 2 3 4 5 1 2 3 4 5
Gray Rami Alone
Non-Medullated Visceral Branches of Sympathetic Chain
Gut (1)
Gut (3)
(2)
Lymph Vessels and Nodes of Gut
(1) & (2) - End Fibers, Parasympathetic
(3) - End Fibers, Sympathetic
(A) Gray & (B) White Rami Communicantes & (C) Spinal Nerves
Stomadeum
Proctodeum
XI XII IX X VII I XIII

Fig. 8.—Schematic drawing to illustrate theory of spread from the gastrointestinal tract.

1. One person may have a marked degree of protection against the gastrointestinal group of organisms and their toxins. Even though the virus is taken into the gastrointestinal tract, such an individual might never get the disease.

2. Another person may be sensitive to the dysentery typhoid paratyphoid or to the colon bacillus factor, but immune to the virus and thus escape the disease.

3. One person may be exposed to an extremely virulent combination of factors, i.e., virus and enteric toxins as in sewage, which when swallowed would produce the disease at once.

4. One may ingest virus which may be nearer the purified state of a fixed laboratory strain. If there is no protection, it would first cause stasis and symptoms; later, it would combine with the enteric toxins of a stased gut and spread over the autonomic nervous system to produce the disease (two-humped; incorrectly termed dromedary).

5. Or the virus in its laboratory phase may enter the gut of an individual whose sympathetic system to the cells of origin has been previously conditioned to gastrointestinal toxins, and when the virus reaches the axis-cylinders, it immediately spreads to the cord.

CONCLUSIONS

I might conclude by stating that it is my belief that poliomyelitis is a peripheral neuritis of the autonomic nervous system, and that the virus enters by way of the gastrointestinal tract. It is a disease probably caused by nonliving entity in the nature of an enzymic catalyst with an almost obligate affinity for the axis-cylinders of gray nerve fibers; a disease, the causative factor of which is a combination of virus and intestinal toxins; a disease possibly checked by normal healthy medullated nerves, as well as by immunologic means; a disease, the happening of which might be termed an accident occurring during the course of mass exposure.

EPOCHAL EVENTS IN POLIOMYELITIS RESEARCH

If one should attempt to estimate the progress of poliomyelitis research, it could be concluded that the epochal events in the past forty years have been: (1) the isolation of the virus from the human being and its transference to monkeys; (2) the demonstration of virus-neutralizing antibodies in the blood sera of convalescent poliomyelitis patients; (3) the evaluation of the pathology of the disease and the acceptance of the conception that nerve cells are destroyed first and that other phenomena follow: (4) the demonstration that the virus spreads along neurones to the central nervous system; (5) the discovery that the virus can be acclimated to some smaller laboratory animals; (6) the fact that the virus can be easily isolated from the stools of patients who have had the disease.

We have conditioned our minds along certain lines for the past forty years. Most of the experiments described during this period have been made in animals given the disease by injecting virus intranasally, intrathecally, intrasciatically, or by some other artificial avenue of approach. If the virus enters the human being by way of the gastrointestinal tract, practically all, except the broader conclusions, especially those that have to do with pathogenesis and the explanation of symptoms, have to be discarded in toto.

It is important to ascertain if the smaller laboratory animals, such as eastern cotton rats, mice, etc., can be acclimated to poliomyelitis virus and used wholesale in experiments. We still need the monkey, however; or, we would still need an animal whose susceptibility can be demonstrated by way of the gastrointestinal tract nearly 100 per cent. When this is accomplished, we may really be able to evaluate convales-

cent serum, for instance, and the various factors pertaining to the gastrointestinal tract which protect certain individuals from contracting the disease.

All of the experiments done during the last thirty years, in which the olfactory, the intracerebral, and other areas were used as the portals of entry, will have to be repeated, using the gastrointestinal tract as the portal of entry.

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American Academy of Pediatrics

Proceedings

MEETING OF THE EXECUTIVE BOARD OF THE AMERICAN ACADEMY OF PEDIATRICS

The meeting of the Executive Board was called to order by the President, Saturday morning, May 31, 1941, at the Orrington Hotel, Evanston, Ill. Those present were:

Dr. Richard M. Smith, President
Dr. E. C. Mitchell, Vice-President
Dr. Clifford G. Grulee, Secretary-Treasurer
Dr. Edgar E. Martmer, Assistant Secretary
Dr. Ernest Caulfield, Historian
Dr. Stanley Nichols, Regional Chairman of Region I
Dr. Hugh Leslie Moore, Regional Chairman of Region II
Dr. Edward B. Shaw, Regional Chairman of Region IV
Dr. Lewis Webb Hill, Associate Chairman of Region I
Dr. Warren W. Quillian, Associate Chairman of Region II
Dr. Lee Forrest Hill, Associate Chairman of Region III
Dr. Hugh K. Berkley, Associate Chairman of Region IV

The following applicants were elected to Fellowship:

Region I

Dr. Montgomery Blair, Jr., Washington, D. C.
Dr. Elizabeth Brakeley, Montclair, N. J.
Dr. Elizabeth Chickering, Washington, D. C.
Dr. Sidney I. Doubilet, Montreal, Quebec
Dr. Aubrey K. Geddes, Montreal, Quebec
Dr. Frank X. Giustra, Brooklyn, N. Y.
Dr. William A. Howard, Washington, D. C.
Dr. J. Albright Jones, Swarthmore, Pa.
Dr. David Klein, Montreal, Quebec
Dr. Benjamin Kramer, Brooklyn, N. Y.
Dr. Kenneth S. Landauer, Geneva, N. Y.
Dr. Joseph L. Lewis, Waltham, Mass.
Dr. John A. Lichty, Jr., Rochester, N. Y.
Dr. William C. McGuire, New Haven, Conn.
Dr. Philip R. Miller, Brooklyn, N. Y.
Dr. Sydney Nussbaum, Brooklyn, N. Y.
Dr. Charles H. O'Regan, New York, N. Y.
Dr. Henry Rascoff, Brooklyn, N. Y.
Dr. Mitchell I. Rubin, Philadelphia, Pa.
Dr. D. William Scotti, New York, N. Y.
Dr. Jessie Boyd Scriver, Montreal, Quebec
Dr. Harry Sherman, Brooklyn, N. Y.
Dr. Charles E. Snelling, Toronto, Ontario
Dr. Irwin P. Sobel, New York, N. Y.

Dr. Louis Spekter, Hartford, Conn.
Dr. William J. Turtle, Boston, Mass.
Dr. Saul J. Usher, Montreal, Quebec
Dr. H. Beril Warshall, Brooklyn, N. Y.
Dr. Herman Yannet, Southbury, Conn.

Region II

Dr. Alexander J. Alexander, Lexington, Ky.
Dr. Joseph R. Bowman, Johnson City, Tenn.
Dr. Charles P. Brown, Norfolk, Va.
Dr. Richard G. Elliott, Lexington, Ky.
Dr. Clarence D. Fowler, Atlanta, Ga.
Dr. Emily Gardner, Richmond, Va.
Dr. Jerome S. Harris, Durham, N. C.
Dr. Alton M. Johnson, Valdosta, Ga.
Dr. R. George McAliley, Atlanta, Ga.
Dr. Henry S. Meyer, Houston, Texas
Dr. Ramsay Moore, Dallas, Texas
Dr. Frank H. Richardson, Black Mountain, N. C.
Dr. Carroll E. Roach, Greenville, Miss.
Dr. Irving Rosenbaum, Jr., Louisville, Ky.
Dr. Harold J. Starr, Chattanooga, Tenn.
Dr. Jack E. Strange, New Orleans, La.

Region III

Dr. Donn J. Barber, Greeley, Colo.
Dr. Rollin E. Cutts, Springfield, Ill.
Dr. George V. Herrmann, Kansas City, Mo.
Dr. Howard M. Jacobs, Chicago, Ill.
Dr. Robert A. Lyon, Cincinnati, Ohio
Dr. Donald N. Medearis, Kansas City, Kan.
Dr. Paul N. Morrow, Omaha, Neb.
Dr. Samuel J. Nichamin, Detroit, Mich.
Dr. Daniel J. Pachman, Chicago, Ill.
Dr. Louise F. Schnute, East Lansing, Mich.
Dr. Isadore B. Silber, Cleveland, Ohio
Dr. Arnold M. Smythe, Des Moines, Iowa
Dr. Albert F. Stein, Fort Custer, Mich.
Dr. Charles A. Tompkins, Omaha, Neb.
Dr. Clarence M. Weidenthal, Cleveland, Ohio
Dr. William R. Whitley, Evanston, Ill.

Region IV

Dr. David B. Davis, Los Angeles, Calif.
Dr. Hertha Ehlers, Los Angeles, Calif.
Dr. Frederick B. Joy, Seattle, Wash.
Dr. Pearl V. Konttas, Santa Rosa, Calif.
Dr. H. Milton Van Dyke, Long Beach, Calif.

Dr. Paul L. Parrish of Brooklyn, N. Y., was transferred from active to Emeritus Fellowship, at his request.

The following were elected to Associate Fellowship:

Dr. Sidney Farber, Boston, Mass.
Dr. Arnold Gesell, New Haven, Conn.
Dr. William E. Ladd, Boston, Mass.

Dr. K. F. Meyer, San Francisco, Calif.
Dr. Albert Montgomery, Chicago, Ill.
Dr. W. H. Sebrell, Washington, D. C.
Dr. L. W. Sontag, Yellow Springs, Ohio

The treasurer's report was discussed and accepted, as was the new budget.

It was moved and carried that in the opinion of the Executive Board, all monies held by the various Regions should be accounted for each year and the accounts audited by an independent auditor; that the funds should be deposited in the name of the Academy and the Region, the account being held in the name of at least two members of the Region who would be empowered to sign checks.

The Executive Board discussed plans and arrangements for the annual meeting in Boston.

The reports of the Committees on Central and South American Scholarships and on Contact Infections were accepted, and their chairmen were congratulated upon their work.

The name of the Committee on Child Health Relations was changed to the "Committee on Cooperation with Governmental and Medical Agencies."

Dr. E. C. Mitchell reported on the Committee on Cooperation with the American Legion. He stated that he felt that the American Legion could help us greatly in education and in controlling unsatisfactory legislation. He felt that we could expect full cooperation from them.

The report of the Committee on Cooperation with Non-Medical Groups and Societies was accepted, and it was decided to print the brochure in full, if possible.

The reports of the following committees were accepted: Committee on Infantile Paralysis; Committee on Medical Education, Post-Graduate Education, Under-Graduate Education; Committee on Mental Health; Committee on National Defense and Relief; Committee on Nursing Education; Committee on School Health and School Health Education.

The report of the Committee on Mother's Milk Bureaus, which reported progress, was accepted.

Dr. Martmer reported at length on the Council for Pediatric Research. His report was accepted and the Committee has empowered it to continue its activities in receiving and placing donations for specific scientific projects, and to act as a consulting body when requested.

It was the opinion of the Executive Board that at least one member of a standing committee should be changed each year, and except under unusual circumstances, the chairman of a standing committee should not be a member of the Executive Board. It was also felt that no man should serve on more than one committee at one time, and that we should, so far as possible, simplify the names of the committees.

Dr. B. J. Berger of Dallas, Texas, and Dr. T. J. McElhenney, of Austin, Texas, were appointed cochairmen for Texas, following the resignations of Dr. William Boyd Reading and Dr. Edwin G. Schwarz.

It was suggested that the Secretary should send a letter of information to the State Chairmen, detailing so far as possible the activities in the various states and matters of general information and assistance.

The following resolution, which was adopted by Region III and Region IV, was approved with the recommendation that it be sent to the Surgeon General of the Army, the Surgeon General of the Navy and the Administrator, Office of Coordinator of Health, Welfare, and Related Defense Activities:

> "Whereas pediatricians are eager to serve in the National Defense Program to the best interest of the Federal Government, and

"Whereas the pediatrician occupies an unusually favorable position, by virtue of his training and experience, with regard to the management of nutritional problems and the problems concerned with sanitation and contagious disease control, therefore

"Be it resolved by the Executive Board of the American Academy of Pediatrics, in session at Evanston, Illinois, May thirty-first and June first, 1941, that the ---------- be respectfully urged to outline the objectives to be fulfilled in the Defense Program by the pediatricians of the nation individually and collectively, and that furthermore

"In the formulation of such a policy for the service, both public and private, of pediatricians to the nation, that their exceptional training in nutritional problems, the care of the contagious diseases, and the supervision of child welfare in the nation be given especial consideration."

There was a discussion of the advisability of establishing a fifth Region within the Academy, consisting of Central and South American Fellows, but it was decided to discuss this more fully at a later date.

The matter of a Children's Tumor Registry was discussed. It was decided that the president should be empowered to appoint a committee of three to investigate the advisability of such a registry and to report in Boston.

Dr. Alexander T. Martin was appointed a member of the Committee on Cooperation with Governmental and Medical Agencies.

Following communication from Dr. George N. Leonard of Miami, Fla., it was decided that the future Directory should contain multiple listings of offices of Fellows in the geographical list only and not in the alphabetical list. This empowers any member having two or more offices to be listed in each office, under the geographical list.

At the request of the Committee on National Defense and Relief and of the Children's Bureau, through Dr. Martha Eliot, the Secretary was empowered to make a list of physicians who have completed one or two years in pediatric service, but who are not eligible to take the examination of the American Board of Pediatrics.

Report of the Committee on National Defense and Relief

The general Committee on National Defense and Relief has been functioning in two lines.

First, a group of the Committee under the subchairmanship of Dr. Joseph S. Wall is working in collaboration with the Children's Bureau in Washington on the general subject of nutrition. Dr. Wall has communicated with all the State Chairmen, asking them to work toward the appointment of a pediatrician on state committees which are being formed or may be formed in each state. Dr. Wall is also following up suggestions made at a committee meeting in New Haven that contacts be made in Washington to try to influence the selective service authorities to exempt pediatricians from the draft. What constitutes a pediatrician while still young enough to be in the draft age and yet not a diplomate of the American Board of Pediatrics is a bit of a problem.

I understood from the conference in Washington that it was specifically suggested that in potential danger zones such as New York City there be a careful census of infants and preschool children and a register prepared thereof, also a checkup on their health conditions, their nutrition status, their presumed cleanliness, and their mental health; and that the same should be done for school-age children. Information should be available on the health and social situation of all the City's children. The transactions of this conference, when obtained, will be closely studied and followed up.

Second, the Committee's activity for the care of refugee children is at pretty much of a standstill except for the chairman who is acting as consultant to the United States Committee for the Care of Refugee Children in the care of some of its present wards, and as medical member of an advisory committee. It is quite certain that no more English evacuées will come in, but it is possible that small groups of continental children may still appear.

Respectfully submitted,
Philip M. Stimson, Chairman.

Report of the Committee on School Health and School Health Education

The proposed bill to subsidize school health programs, mentioned in the report of November, 1940, died in committee and was replaced by the Schwert Bill (HR 1074) in the Congress in 1941.

The discussion of these two bills has brought into clearer focus the controversy as to whether the school health program should be administered by the health department or the education department. Many of the larger cities have continued with the control in the health department. Education department control is more prevalent among the smaller cities. More recently county health departments have given leadership on the school health program in rural schools. Social Security legislation has been favorable to an extension of health department control in the rural and village schools. With such an extension of health department leadership, the school authorities have been aroused to seek federal legislation to obtain subsidies with education department control.

This competition for administrative control is unfortunate because the best health education and guidance toward sound medical service has been achieved through the close cooperation of the educational authorities, the health department, and the medical practitioners. There is no real indication that better teamwork is achieved with one form of administrative control than another. Competition between two departments or professional groups is a serious threat to progress in our democratic system. It overemphasizes differences and spreads confusion even where there is actual agreement on policies.

Both the health authorities and the educational authorities recognize that health education is primarily a teaching function and the teacher is the "key" person for health instruction. Both groups recognize that physical education is a function of the education department. But the part of the physician and nurse in the schools is not so clearly a service that should be controlled by educators even though we regard it as fundamentally an educational function. It is obviously a function that is dependent upon the other community medical services for its successful operation. Its educational objectives are concerned with the individual education of parents and children rather than with the education of the child in the classroom. Such education, then, is a function to be shared with the practicing physician rather than education that is carried out altogether in the schools. Health departments are more and more recognizing the necessity for coordination and cooperation between the school and other community medical facilities, and have set up the mechanism for utilization of medical facilities already established. Education departments, on the other hand, have had a tendency to neglect the teaching of individual responsibility for medical care. They have not made people aware of the medical services that are available in the community. They have not stimulated nor guided individual decisions as to how to get medical services. Too often education department leadership has fostered a dependence upon public services. They have lacked an understanding of what is meant by "individualized medical care" and "health supervision." Education department control has not been characterized by sound medical influence on education as to the use of medical facilities.

While Health department leadership of the physician and nurse part of the school program generally facilitates coordination with all community medical resources, it is obvious that progress in the school health program cannot be achieved with a deadlock between two departments or professional groups. If a complete change of administrative control away from the education department is not acceptable, then some scheme must be developed for medical influence and sound leadership within the education department or through cooperation with the health department and medical profession. In any case, there should be an administrative plan for coordination with the other community medical facilities.

The distribution of funds controlled entirely by an education department should always be safeguarded so that medical responsibilities may be borne by the medical profession. While a special board or a joint responsibility of two departments for the administration of funds or subsidies concerned with the physician's and nurse's part in the school health program is cumbersome, there is a growing recognition that the school health program should have both the educational and medical professions participating on an equal basis, and this cannot be achieved through competition for administrative control. The attitude of the American Public Health Association toward the Schwert Bill reported in the *American Journal of Public Health* in February, 1941, is consistent with the opinion outlined above.

Harold H. Mitchell, Chairman.

PEDIATRICS AND NATIONAL DEFENSE

Pediatrics in the Defense Program*

Frederick F. Tisdall, M.D.
Toronto, Ontario

I appreciate greatly the invitation of your program committee to sit in at this informal discussion this evening on pediatrics in the defense program, and to tell you of our experiences in Canada. I will attempt to be very brief—I hope successfully—and just outline to you the highlights of what we have done, and then if any further information is desired, no doubt it can be brought out in the discussion.

Within a few days of the outbreak of war in September, 1939, it was realized that some measure should be set up to insure not only adequate medical personnel for the newly formed armed forces, but also adequate personnel for the civilian population. Accordingly, the Canadian Medical Association met with the government and arrangements were soon consummated whereby any requests for medical personnel for the Army, the Navy and the Air Force went through the Canadian Medical Association office. In this way care has been taken to insure that the services of the medical men of Canada were utilized to the best advantage from a national standpoint. It was realized from the beginning that a great waste would occur if men with special training for either civilian or army medicine were used for routine army work. I will show you later where the pediatrician fits into this whole scheme of things.

Within five weeks of the outbreak of war, at a meeting of the Dominion Council of Health at Ottawa, Dr. Alan Brown, consultant on pediatrics to the Dominion Department of Pensions and National Health, drew to the attention of this department the need for expansion rather than any restriction of the activities of the government agencies in regard to the care of the child. He emphasized that experience during the last war, when both the government and private charities restricted their child welfare work, showed that the amount of sickness and the mortality rate among infants and children were markedly increased. This is a problem of very real concern to the pediatrician, and in Canada every effort has been made to draw to the attention of the proper authorities the absolute necessity of not only maintaining but extending child welfare work. To give you some idea of the problem before us, at the present time 44 per cent of the national income of Canada is being spent on the armed forces and materials for their use. The same percentage of the national income of the United States is $35,000,000,000. Taxes on the middle and the well-to-do classes have increased by leaps and bounds. Greater calls have been made for war charities, and then there is the drive to put every possible cent of savings in War Savings Certificates. As you can readily see, this makes much less money available for the so-called peacetime charities such as children's hospitals, welfare stations, and other agencies helping in the care of the infant and child. We are happy to say that in Canada to date there has been no restriction in the activities of these welfare agencies, as is well evidenced by the fact that for the year 1940 the infant death rate in the city of Toronto was the lowest in its history, 39.1 per 1,000. Also, during the past year there has not been a single case of diphtheria in Toronto, with a population of approximately three-quarters of a million people, and the incidence for the whole of the province was only 0.6 per 100,000.

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*Presented at the annual meeting of Region I of the American Academy of Pediatrics, New Haven, March 27, 1941.

One word in regard to the care of the evacuated children from Great Britain, because this care illustrates the close cooperation between the pediatrician and governmental and volunteer organizations in Canada. A plan was prepared by Dr. Alan Brown in his official capacity as consultant in pediatrics to the Provincial Department of Health, which was adopted in Ontario and was accepted with minor modifications by the other eight provinces of the Dominion. The plan for Ontario was under the direction of the Provincial Department of Health and the Provincial Department of Welfare. On arrival in Ontario, all the children came to the city of Toronto and were then housed by the Department of Welfare. They were not only examined by the officials of the Department of Health but were also all brought to the Hospital for Sick Children, where they were examined by the pediatric staff. X-rays were taken of all the children, diphtheria toxoid was administered to all, and other tests were made and treatments given as indicated. All the facilities of the Hospital, including the special clinics, were placed at the disposal of the Departments of Welfare and Health. It was felt essential that diphtheria toxoid should be administered to all the children, due to the fact that in Great Britain the incidence of diphtheria last year was 39 per 100,000 as compared to 0.6 per 100,000 in Ontario. After a clean bill of health was given to the children, they were placed in homes through various Children's Aid Societies. The facilities of the Hospital for Sick Children have been extended to these organizations.

It is obvious of course that the pediatrician has a most important part to play in looking after the welfare of the infant and child during wartime as well as peacetime, but there is another most important role for the pediatrician in the program of national defense, and that is nutrition. Of all groups of physicians or specialists, none have studied so thoroughly the fundamental principles of nutrition as have the pediatricians. Consequently, the pediatricians can be the leaders in any nutrition work viewed from the national standpoint. Unfortunately, in the past I believe that in Canada many of our pediatricians have utilized their knowledge on nutrition entirely from the standpoint of the individual patient. But it is not difficult to extend this interest to include nutrition from a national standpoint. The same principles apply to the nutrition of the adult as to the nutrition of the child, and it is well known that with the increased industrial activity of wartime, the nutritional requirements not only for calories and proteins and fats but also for vitamins and probably minerals are increased.

What work is being done along these lines by the pediatricians in Canada? First of all, the work that is being done can be divided into two classes: (1) special research work, and (2) educational work. In regard to research work, I will tell you of two activities, for example, being carried on in our laboratories at the Hospital for Sick Children and the University of Toronto. Dr. Drake has been investigating the supply of vitamin C from a national standpoint, and he has found a lot of information of value to a nation at war. First of all, he has made the rather surprising finding that there is no appreciable amount of vitamin C in apples, pears, peaches, cherries, green grapes, celery, iceberg lettuce, hothouse leaf lettuce, and some of the other green salad vegetables. He finds that the supply of vitamin C is much more restricted than we had any idea, and it is not enough to tell the population to eat lots of fruit and raw vegetables. You have to specify the rich sources, which from the Canadian standpoint are the citrus fruits, tomatoes, cabbage, turnips, and freshly picked summer spinach and Swiss chard. All this work is being done in cooperation with the provincial Department of Agriculture.

The second example of work being done by our laboratory is on Canadian wheats and flour, in cooperation with the Federal Department of Agriculture. As you know, surveys and studies conducted in the United States and in Canada have indicated that a large proportion of the people are not receiving the amount of the

various B vitamins necessary for optimum health. We have long since got away from the idea that deficiency diseases such as beriberi, pellagra, rickets, and scurvy are the great problems. These are simply the end results of a marked deficiency and in Canada are under good control, as is evidenced by the fact that in the year 1925 we had 154 cases of rickets at our hospital which averages over 100,000 attendances a year, while ten years later we had only four cases. Some two years ago, when Sir Edward Mellanby, Secretary General of the Medical Research Council of Great Britain, was visiting us, he was greatly impressed when the staff was called together to see a case of rickets as a medical curiosity. He commented on this in his annual report. As I have said, we are much more concerned with the minor deficiencies which interfere with optimum efficiency and optimum health, and it is evident that to have the nation work at its maximum efficiency it must have optimum amounts of all the food elements. A lack of the various members of the vitamin B complex is apparently quite widespread. How can this best be corrected? Wheat is an excellent source of many of the B vitamins. Yet unfortunately in the milling process five-sixths of the vitamin B_1 is removed and a large percentage of the other B vitamins. So here at once is a problem. How can wheat be milled so that it will retain the B vitamins in a much larger amount than is at present the case with white flour. This is the problem with which we have been working in conjunction with Dr. Newman, Chief of the Cereal Division of the Department of Agriculture at Ottawa, and some of the millers. I am happy to say that we have succeeded in producing a white flour—not an "off color" flour, but a white flour—which retains two-thirds of the vitamin B_1 originally present in the wheat, and an increased amount of the other members of the B complex. To give you an idea of what this may mean, if this flour were used in place of the ordinary white flour in Canada, it would give the people of Canada during the course of one year, for nothing, at drugstore prices, $26,500,000 worth of vitamin B_1 alone, as well as valuable amounts of the other members of the B complex. Steps are under way to put these findings into practical effect.

The second role that the pediatrician can play in regard to national nutrition is in educational work on nutrition. In Canada the pediatricians have taken a very active part in this, largely through the Canadian Medical Association. Just before the war broke out, a booklet was produced, "What to Eat to Be Healthy," and 1,250,000 of them were distributed by the Canadian Medical Association with the financial assistance of the Life Insurance Companies in Canada, at no cost to the Canadian housewife. Just a year ago a second booklet was prepared, "Food for Health in Peace and War," telling the housewife how she could best spend her money to get optimum nutrition at the lowest cost. This booklet was also produced by the Canadian Medical Association, and with the assistance of the Life Insurance Companies in Canada and the Canadian Red Cross 1,750,000 of these have already been distributed, and an additional three-quarters of a million are being printed as a second edition. This makes in all two and one-half million copies. The total number of homes in Canada is estimated to be just two and one-half million. Another activity in which the pediatricians in Canada played a considerable part was the preparation of colored posters for the schools on "What to Eat to Be Healthy." These posters were issued under the auspices of the Canadian Medical Association, with the financial assistance again of the Life Insurance Companies in Canada.

The pediatrician could take a very active part if he so desired in the local campaigns in regard to nutrition. This has been done in Toronto during the past year, and early next month a nutrition campaign is being launched in the city of Winnipeg. The pediatricians in Canada are taking part in this activity.

As mentioned earlier, I believe it can be said truthfully that in Canada the various government authorities as well as charitable organizations are regarding the pedi-

atrician not only as one who deals with children but also as one who has special knowledge on nutritional subjects. For instance, the Canadian Red Cross has undertaken to supply this year 10,000 food parcels per week for the British prisoners of war in Germany. This involves a cost during the year of $1,500,000, or approximately one-quarter of the amount raised by the Red Cross in its last campaign. The parcel has been very carefully planned to supply in the space available the maximum amount of food values possible, taking into consideration not just fats and carbohydrates and proteins but also minerals and vitamins, in the most acceptable form possible for man. Pediatricians in Canada were consulted and asked to take the responsibility for the selection of the food articles to go in this parcel.

It may be of general interest to you to know that these parcels are being packed by voluntary workers, about thirty to thirty-five women working each day. Two traveling belts or assembly lines have been set up and the food boxes go down these lines and each worker puts in one or two articles of food. Two thousand packages are packed and sealed each day at the rate of thirteen a minute, so that the packing is all done in about three hours' time. I may say it is strenuous work while it lasts. The packages are then shipped to New York, on to Lisbon in Portugal by the American Export Line, and then are carried by Portuguese coastal boat past Gibraltar to Marseilles, France, where they are shipped to the International Red Cross at Geneva, Switzerland, and then distributed by the International Red Cross in Germany.

In conclusion, it is of interest to note that the military authorities in Canada are aware of the importance of applying modern knowledge on nutrition to the feeding of the armed forces. Accordingly they have appointed a consultant or adviser on nutrition—who incidentally happens to be a pediatrician—to the Department of National Defense. I may say that in all this work we in Canada are greatly indebted for the help and advice we are constantly requesting and which you, our confreres in the United States, are so generously giving.

Army and Navy Appointments

Dr. James E. Bowman of Philadelphia is a lieutenant in the Naval Reserve, and is, at present, in the Philadelphia Naval Hospital.

Dr. R. Cannon Eley of Boston is a lieutenant-commander in the Navy, at present teaching in the Surgical Department of the Navy in Boston.

Dr. Paul W. Emerson of Cheyenne, Wyo., has been appointed pediatrician on the State Nutrition Committee, elected president of the Reserve Officers Association, Cheyenne Chapter, and as lieutenant-colonel, has been assigned to the 171st Station Hospital, R.A.O.G.H.Q.

Dr. Robert A. Strong of New Orleans has been called to active duty with the Army, with headquarters at the Third Military Area in New Orleans.

Dr. Max Deutch of St. Louis is now a captain in the Medical Corps, 161st Infantry, A.P.O., Tacoma, Wash.

Dr. Joseph Stokes, Jr., of Philadelphia, Pa., is Director of the Commission for the Control of Measles, Consultant to the United States Army under the Board for the Control of Epidemic Diseases. He is also a member of a special committee of the American Institute of Nutrition for the study of the program for emergency relief rations for Europe.

Academy News

The following applicants have been elected to Fellowship in the American Academy of Pediatrics since the meeting of the Executive Board:

Dr. Helen F. Aff-Drum, Clayton, Mo.
Dr. Peter G. Danis, St. Louis, Mo.
Dr. Joseph C. Jaudon, Webster Groves, Mo.
Dr. Louis E. Payne, Toledo, Ohio
Dr. Harold E. Petersen, St. Joseph, Mo.
Dr. Sherl J. Winter, Dayton, Ohio

An important feature of the annual Academy meeting in Boston, Oct. 9 to 11, 1941, will be the scientific exhibits. Members wishing to display material should communicate at once with Dr. Clement A. Smith, 300 Longwood Avenue, Boston, Mass.

Through the influence of members of the Academy in Montreal, a committee of the pediatric section of the Montreal Medico-Chirurgical Society has been formed for the purpose of establishing facilities for the medical examination of household workers. It is hoped that within the next month or two any employer who desires may be able to have household workers examined prior to employment, the examination to consist of a chest film, a Wassermann test, and a physical examination.

In Kansas there has been some work done in connection with child guidance and maternal welfare work in connection with the state society and crippled children's work. In Wichita a general P.-T.A. preschool roundup has been carried on quite successfully, with a great number of children examined and immunized for diphtheria, and a large number of tuberculin tests given with P.P.D. No. 2.

The Mississippi State Pediatric Society held its regular meeting on Monday afternoon and evening, May 12, 1941, at Biloxi. Dr. George M. Lyon of Huntington, W. Va., was the guest speaker. Dr. Harvey F. Garrison, Jr., gave the report of the Region II meeting at Richmond. Dr. Harvey F. Garrison, Sr., was recommended unanimously for State Chairman.

The American Academy of Pediatrics of Illinois has carried on several important activities through its various committees during the past year. The booklet compiled on preventive pediatrics has been published and is now being distributed to all physicians in Illinois by the Illinois Department of Health.

The Contact Infection Committee is continuing its activities in attempting to establish a system of yearly examinations of school teachers and domestic servants. Progress in this work has been slow, but programs now have been instituted in LaGrange and in the North Shore suburbs through the cooperation of the various health departments. This committee is particularly interested in securing the cooperation of the various branches of the Chicago Medical Society through members of the Academy in these branches. The plan as now operating in several communities consists of regular yearly examinations which include laboratory tests and

x-rays as indicated. A record of each individual is kept on file in the health department in the community in which he resides. It is to be hoped that with these communities as a starting point, the plan will eventually become state-wide in its operation.

The School Health Committee has now under consideration a plan to institute yearly examinations of all school teachers, with the expense of these examinations carried by the respective school boards. Excellent cooperation with this plan has been reported from several communities.

The committee on Mental Hygiene and Aid to the Mentally Handicapped Child has been actively engaged in two projects during the year, one having to do with the development of a state program for educable mentally handicapped children, the other concerning the formation of a state program for mental health.

In cooperation with the Illinois State Medical Society, State Board of Welfare Commissioners, State Congress of Parents and Teachers, Illinois Society for Mental Hygiene, Illinois Federation of Labor, Chicago Pediatric Society, Chicago Neurological Society, Chicago Woman's Club, and many other local societies and individuals, the committee has worked out a state program for educable mentally handicapped children. This program was incorporated in Senate Bill No. 367. This bill has just passed the senate by a unanimous vote and probably will be voted on by the house this week. Representatives of the Committee on Aid for the Mentally Handicapped Child have cooperated with the Child Hygiene Division, State Department of Health, and the Coordinating Committee of State Agencies in developing a state mental health program. Dr. Jacob Krafft, Dr. Bert Beverly, and Dr. Abraham Levinson deserve great commendation for their untiring work in this project.

Dr. Gerad Cline, chairman of the Committee on Pediatric Care of Crippled Children, reports the following:

The Pediatric Subcommittee of the Advisory Committee to the Commission for Handicapped Children, now under the Department of Public Welfare, met at the Sherman Hotel, Sunday, May 11, 1941. Mr. Lawrence J. Linck, executive secretary, reported that the Budget Committee had approved a $25.00 fee for pediatrician's service at the various clinics held by the Division for the Handicapped Children throughout the state.

Dr. Orville Barbour of Peoria has been the only pediatrician so far used in one of these clinics. He worked with Dr. King of Peoria at the Monmouth Clinic. Dr. Barbour was present at our committee meeting and gave the following report in person:

1. The number of children to be examined will run from fifteen to forty in the bigger clinics.

2. A careful examination of these children might questionably slow up the work of the orthopedic men at the clinics.

3. He found a great need for the pediatrician's services, particularly because of nutritional problems.

4. He did not attempt to explain to the parents anything about the child's condition or advise as to the aftercare from a pediatric standpoint. His report was to be carried back to the referring doctor by the nurse in charge and the diet and treatment to be prescribed either by the referring doctor or the nurse if there is no referring doctor in the case.

5. There was no record form used.

6. He definitely felt that it would be better in the future to take three or four children at a time and run them through fully rather than trying to do it all in one day.

The Pediatric Subcommittee then, after discussion, made certain recommendations to the Advisory Committee, as follows:

1. That the budget for the coming year, beginning June 1, allow the attending pediatrician at the clinic $25.00 for his services plus all expenses for the day. This may run either as 5 cents a mile or railroad fare.

2. That a stenographer be supplied to the pediatrician at each clinic, who will be able to take down his findings and follow up with referral letters to the referring doctor for future care.

3. That the pediatric men conducting the clinics be licentiates of the American Board of Pediatrics. (However, on examining this list we find so few in the downstate area that we feel it will be necessary to grade the different pediatricians as to the qualifications and thereby use some who are not members of the American Board.)

4. That the Subcommittee composed of Dr. Hess, Dr. Black, and Dr. Cline construct a record form to be used at the clinics.

5. That there still remains some question as to who will pay for such things as cod-liver oil, vitamins, etc., that the children need. The Division does pay for the casts used on orthopedic problems so perhaps something will be worked out for the medication.

6. That diet lists furnished by the Child Bureau will probably be given to the patients.

7. That x-ray and blood examinations, if necessary, be done in the local hospitals, paid for by the Division.

8. That the Subcommittee made requisition for the following equipment: scales, records, diet slips, tongue depressors, sphygmomanometer, Vollmer tuberculin tests, tuning fork, and sight charts.

The Subcommittee will complete its report, no doubt within the very near future, so that we hope the new budget, beginning in June, will allow the requests given in the report; if so, it will be only a matter of a short time before the orthopedic clinics now being held will also have a pediatrician conducting a pediatric examination at these clinics. The rate of $25.00 a day with expenses will in a great many instances just about equal that given for their services to the orthopedic men, who receive $50.00 a day and pay their own expenses.

Another of the chief accomplishments of the Academy during the past few months has been the organization of the Coordinating Committee on Child Health for the state of Illinois. Fifteen different organizations interested in child health programs are represented on this committee which also includes five members of the Academy. Dr. Clifford Grulee is chairman and Dr. Rollin Cutts, secretary. After several meetings this committee has drawn up a comprehensive health program to be state-wide in its application. The program is to cover seven different fields.

As the work goes on, representatives from other organizations interested in child health will probably be added to the committee. As one may see from the outline, the project will require a tremendous amount of work and organization by this committee, but in the end its effect should be far-reaching, in that health programs for children, which in the past in this state have been more or less disorganized, will through the work of this committee become comprehensive and coordinated. Much overlapping and repetition of present effort will be done away with. The Academy should play a very important role in this work and our various committees will be called upon from time to time to cooperate with the various subcommittees of the coordinating committee in their task of organizing and planning.

News and Notes

The eighteenth annual meeting of the **Canadian Society for the Study of Diseases of Children** was held at Brockville, Ontario, Saturday, June 14, 1941. Dr. L. M. Lindsay was president.

At the annual business meeting of the **Texas Pediatric Society,** held in Fort Worth, Texas, Tuesday, May 13, the following officers were elected for the ensuing year: president, Dr. P. E. Luecke, Dallas; president-elect, Dr. F. H. Lancester, Houston; and secretary-treasurer, Dr. John Ashby, Dallas. The next meeting of the Society will be Oct. 3 and 4, 1941, in Dallas.

At the thirteenth annual meeting of the **Louisiana State Pediatric Society** in Shreveport, La., April 21, 1941, the following officers were elected for the ensuing year: president, Dr. Julian Graubarth, New Orleans; vice president, Dr. W. B. Worley, Shreveport; and secretary-treasurer, Dr. W. C. Rivenbark, New Orleans.

The **Eighth Pan American Child Congress** will be held in Washington from March 28 to April 4, 1942.

Dr. Thomas D. Jones, of Richmond, Va., assistant professor of pediatrics at the Medical College of Virginia, died of acute lymphatic leucemia, on June 12, 1941.

Dr. A. S. Root of Raleigh, N. C., has been appointed chairman of the Committee on Infant and Maternal Welfare of the State Medical Society.

Dr. Charles R. Bugg of Raleigh, N. C., has been appointed to the State Nutrition Committee.

Dr. John Giblin of Manchester, N. H., has been appointed to the staff of the Sacred Heart Hospital as physician in charge of the pediatric department.

Dr. Sam Phillips of Little Rock, Ark., has been elected president of the State Pediatric Society.

Dr. E. C. McMullen of Pine Bluff, Ark., has been placed on the local exemption board as examiner.

Dr. Park J. White of St. Louis is vice-president and medical representative on the Dairy Council, of St. Louis.

Dr. R. R. Struthers, professor of pediatrics at McGill University, is giving a series of lectures on pediatrics at the summer school of the Vancouver Medical Society in Vancouver, B. C., during the week of June 16, 1941.

Dr. Douglas D. Martin of Tampa, Fla., has been added to the Committee on National Defense and Relief.

Book Reviews

Play for Convalescent Children in Hospitals and at Home. By Anna Marie Smith, A. S. Barnes & Co., New York, 1941, pp. 132. Price $1.60.

There has been a growing appreciation that sick children in the hospitals and at home need something more than skilled medical care to bring them back to health. While the technical medical care is primary in importance, recovery cannot only be aided but hastened and various types of invalid reactions can be prevented if the children are treated as human beings, so to speak, rather than pathologic specimens for the exhibition of medical skill. Thus occupational therapy, play, and the development of normal interests have a distinct and valuable place and field in pediatrics.

Miss Smith, a trained and experienced recreational worker, with many years of work with convalescents, has written this book based on a six years' experience at the Children's Memorial Hospital in Chicago, where an integrated full-time program of play has been in force. As a part of the education in pediatric nursing, courses have been given to the nurses and a large volunteer group has been trained and supervised. The volume includes chapters on play activities and their use, as, for example, play with patients before surgical operations. Suggestions are made as to material and special equipment. An excellent classification of various types of play is given—card games, pencil and paper games, table and board games, and the like. Full references to source material together with an excellent biography make the book of special value. It is by far the best book of this type that has been published and is distinctly practical. It is to be hoped that the book will be carefully read by staff members as well as the nursing heads in our children's hospitals. It is not unreasonable to believe that a better knowledge of play and recreation for children, even perhaps at the expense of some course in bacteriology or kindred subject, would make our nurses far better able to cope with pediatric nursing.

Manual of Clinical Chemistry. Miriam Reiner, M.Sc. New York, 1941, Interscience Publishers, Inc., pp. 295. Price $3.00.

This manual, written by the Assistant Chemist to the Mount Sinai Hospital, New York, is an outgrowth of a mimeographed manual prepared for the use of the house staff and students at the hospital. It presents in a direct, clear way, in readable type, all of the chemical tests used at the hospital for the clinical examination of the blood, urine, feces, cerebrospinal fluid, and for gastric analysis. In addition, it contains chapters on chemotherapy determinations, vitamins, and functional tests. As a rule, only one test is given, which is usually the one in general use at present. It is a decidedly practical and useful book for the hospital laboratory.

Plague on Us. Geddes Smith. New York, 1941, The Commonwealth Fund. Price $3.00.

This is a story of plague and pestilence as it has affected mankind, and man's effort to prevent the devastating effects of epidemics. In as nontechnical a way as possible, and with a delightful style, the author tells the story of past epidemics, the host, the infective agent, and the defenses against infection. The chapter on localized outbreaks, entitled "Detective Work," is particularly commendable, with its subtitles such as "The Case of the Methodist Ladies," in

which a typhoid epidemic in California is described; and "The Case of the Plumber's Patchwork," which tells the story of the epidemic of amebic dysentery which started at a Chicago hotel during the World's Fair in 1933. In a final chapter entitled "Unfinished Business," the author discusses the common cold, tuberculosis, malaria, yellow fever, and plague. While the volume is designed for lay reading, it will be of much more value and interest to physicians, and it should be placed on the reading list for medical students, as it presents the essential knowledge and facts of epidemiology in a vivid, delightful way which cannot help but leave a lasting impression. We need more books like this.